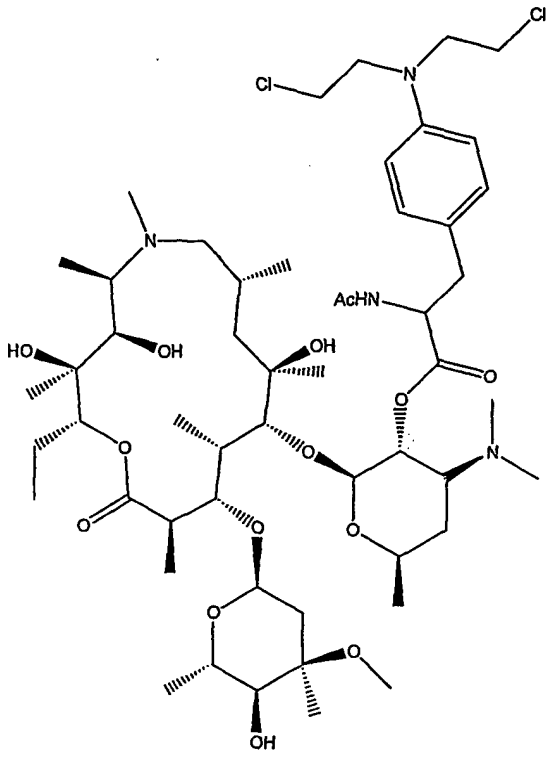
EXAMPLE 20: COMPOUND 62

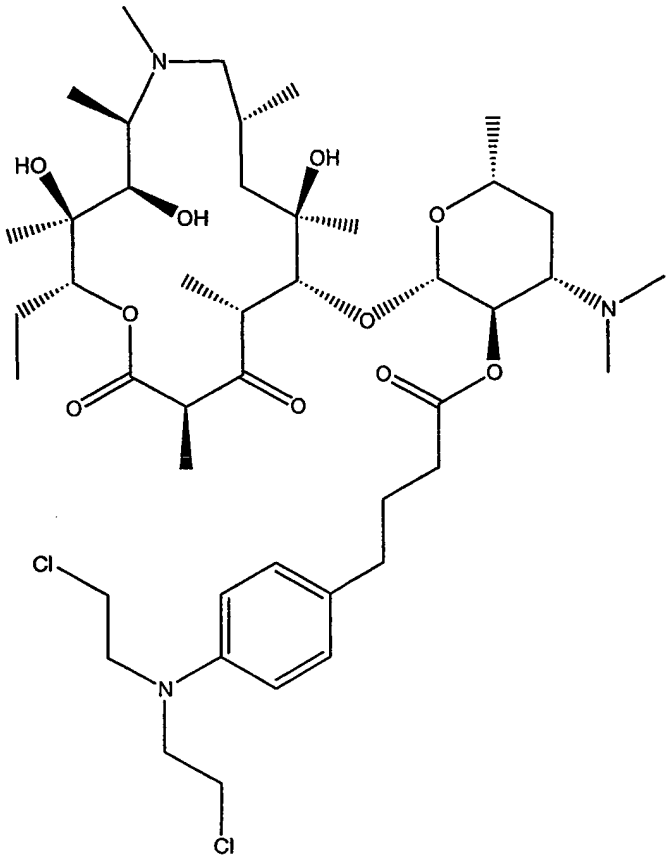


600 mg of melphalan (**63**) is suspended in 25 ml of water containing 500 mg of sodium carbonate. 10 ml of dioxane is added and 1 ml of acetic anhydride. After stirring at ambient temperature for 1 h citric acid is added and the mixture extracted with ethyl acetate. After washing with water and brine the organic phase is dried (sodium sulfate) and concentrated in vacuum. Removal of all volatiles yields the crude N-acetylmelphalan that is carried on to the next step without further purification.

A solution of N-acetylmelphalan (0.35g; 1.0 mmol) dissolved in methylene chloride (5ml), is treated with N,N′-carbonyldiimidazole (0.17g; 1.0 mmol). After stirring for 30 min. at RT, Compound 43 (0.29g; 0.50 mmol) is added. After 3 h the reaction solution is concentrated in vacuum and the residue purified by column chromatography on silica gel, elution with chloroform/isopropanol/methanolic

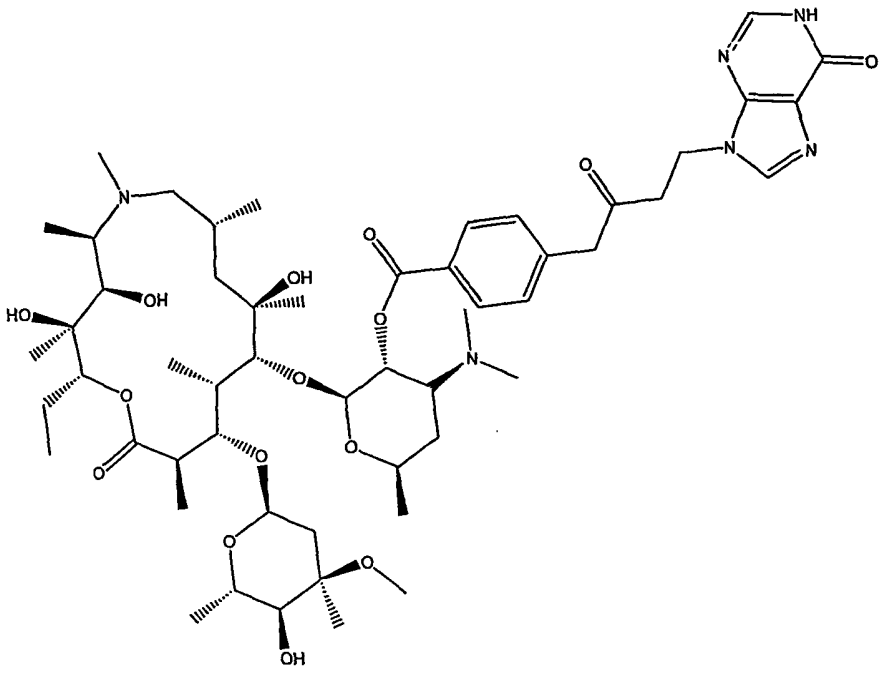
ammonia 60:1:1. The appropriate fractions are collected and concentrated to produce 0.12 g (25%) of Compound 62 as a white foam.

EXAMPLE 21: COMPOUND 64



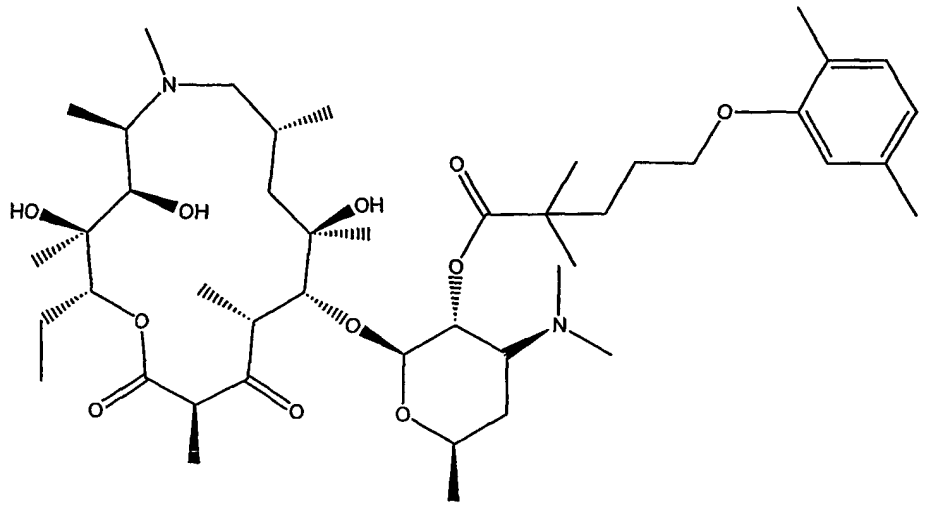
To a solution of chlorambucil (303 mg;1 mmol) in methylene chloride (5 ml), is added N,N′-carbonyldiimidazole (130 mg; 1 mmol). After 30 min stirring at ambient temperature, Compound 43 (750 mg; 1 mmol) is added. After stirring at the same temperature for 3 h the mixture is washed with ice water and ice cold Na_2CO_3 solution. The organic layer is dried (Na2SO4), concentrated in vacuum and chromatographed on silica gel, elution with isopropanol to afford 207 mg (20%) of a white foam, Compound 64, MS ($M+2H^+$: 517).

EXAMPLE 22: COMPOUND 65



A suspension of neotrofin (0.73g; 2.25 mmol) in methylene chloride (15 ml), is treated with N,N′-carbonyldiimidazole (0.38g; 2.25 mmol). After stirring for 2 h at ambient temperature Compound 43 (0.57g; 0.75 mmol) is added. Reaction is stirred for 48 h at ambient temperature. The reaction solution is concentrated in vacuum and the residue purified by column chromatography on silica gel, elution with chloroform/isopropanol/methanolic ammonia 60:1:1. The appropriate fractions are collected and concentrated to produce Compound 65 (0.20g; yield: 25%) as a white foam.

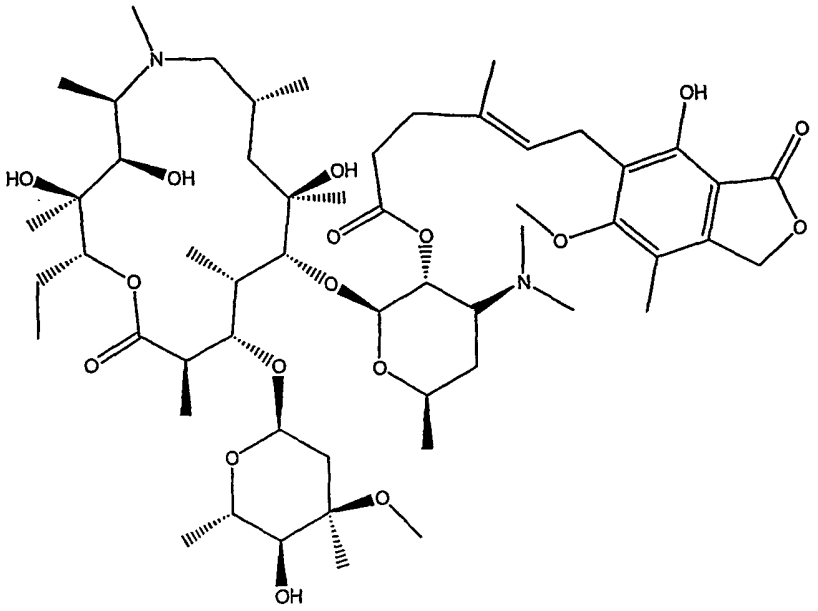
EXAMPLE 23: COMPOUND 66



A solution of Gemfibrozil (0.56g; 2.25 mmol) in methylene chloride (10ml), is treated with N,N′-carbonyldiimidazole (0.38g; 2.25 mmol). After stirring for 30 min. at ambient temperature, Compound 40 (0.44g; 0.75 mmol) is added. Reaction is stirred for 48 h at ambient temperature. The reaction solution was concentrated in vacuum and the residue purified by column chromatography on silica gel, elution with chloroform/isopropanol/methanolic ammonia 60:1:1. The appropriate fractions are collected and concentrated to produce Compound 66 (0.15g; yield: 25%) as a white foam.

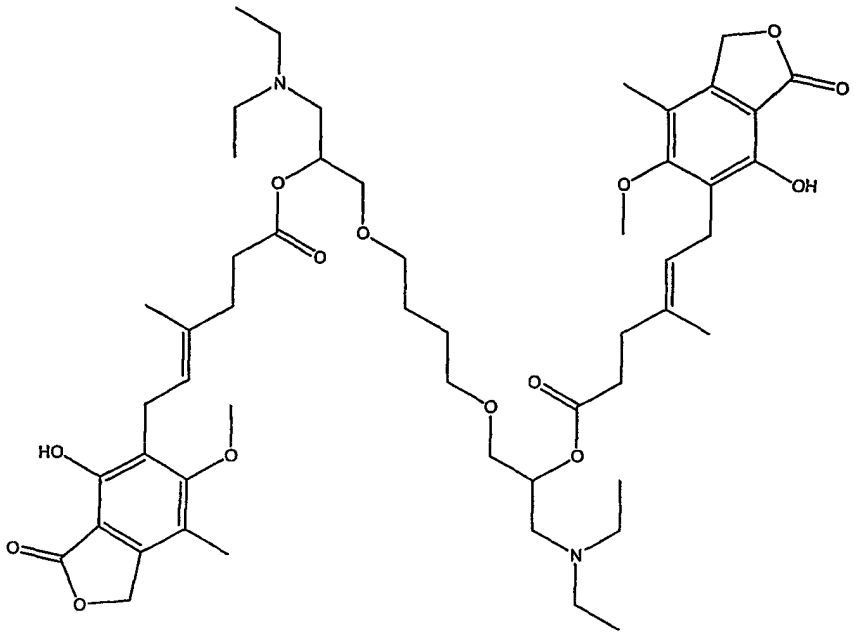
EXAMPLE 24: MYCOPHENOLATE DERIVATIVES

Compound 67



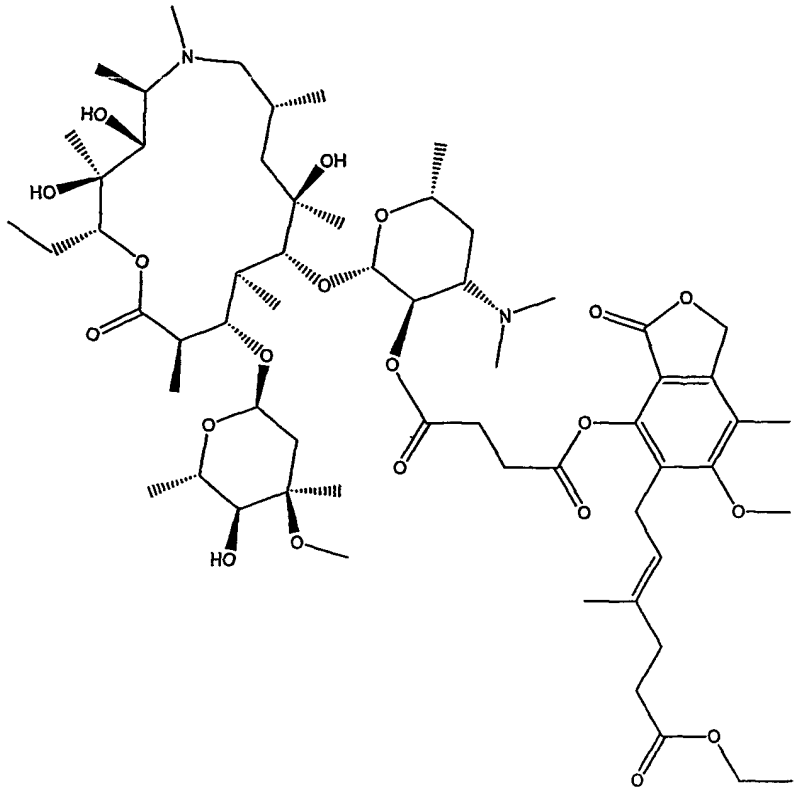
To a mixture of 375 mg of Compound 43, 400 mg of triphenyl phosphine and 960 mg of mycophenolic acid is added 4 ml of THF under nitrogen. Diisopropyl azodicarboxylate (0.3 ml) is added drop wise at 0°C within 4 h while the reaction mixture is rapidly stirred. Cooling is continued for another 4 h and the mixture then allowed to warm to ambient temperature within 5 h. The mixture is then dissolved in a mixture consisting of 50 ml of toluene and 20 ml of ethyl acetate and extracted with ice-cold 0.5 M hydrogen chloride (3 x 150 ml). The aqueous phase is washed several times with small amounts of toluene and then with potassium carbonate till no foaming occurs any more upon addition. The mixture is extracted with dichloromethane and the organic phase is washed with brine, dried and concentrated in vacuum to yield white solid foam that can be used without further purification, or further purified on a silica gel column, eluting with isopropanol.

Compound 68



To a solution of 170 mg of Compound 41, 400 mg of triphenylphosphine and 500 mg of mycophenolic acid in 3 ml of THF were added under nitrogen 0.3 ml of diisopropyl azodicarboxylate within 4 h at 0°. The mixture was allowed to stir at 0°C for 3 h and was then allowed to warm to ambient temperature slowly. The reaction mixture was diluted with 70 ml of toluene and 30 ml of ethyl acetate and extracted repeatedly with ice-cold 0.5 M hydrogen chloride. The combined aqueous phases were extracted several times with a small quantity of toluene. The organic phases were discarded. The aqueous phase was treated with potassium carbonate till gas evolution had stopped and was then extracted with dichloromethane. Drying (sodium sulfate) and concentration in vacuum yielded an oily residue that was purified by filtration through a short pad of silica gel (elution with ethyl acetate-triethylamine) to afford 185 mg (39%).

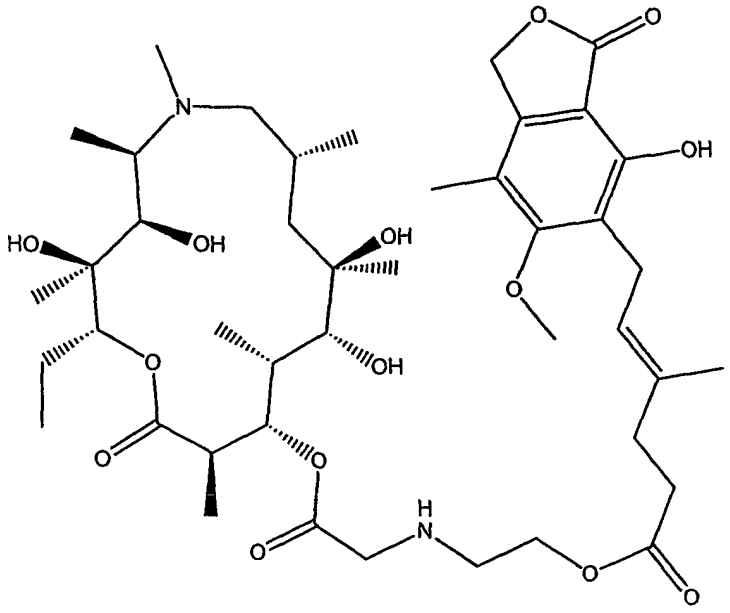
Compound 69



A solution of 750 mg (1.0 mmol) of Compound 43 in 10 ml of dichloromethane is treated with 100 mg (1.0 mmol) of succinic anhydride. After stirring at ambient temperature for 12 h the mixture is concentrated in vacuum to yield Compound **70**, a colorless solid that is used with out further purification.

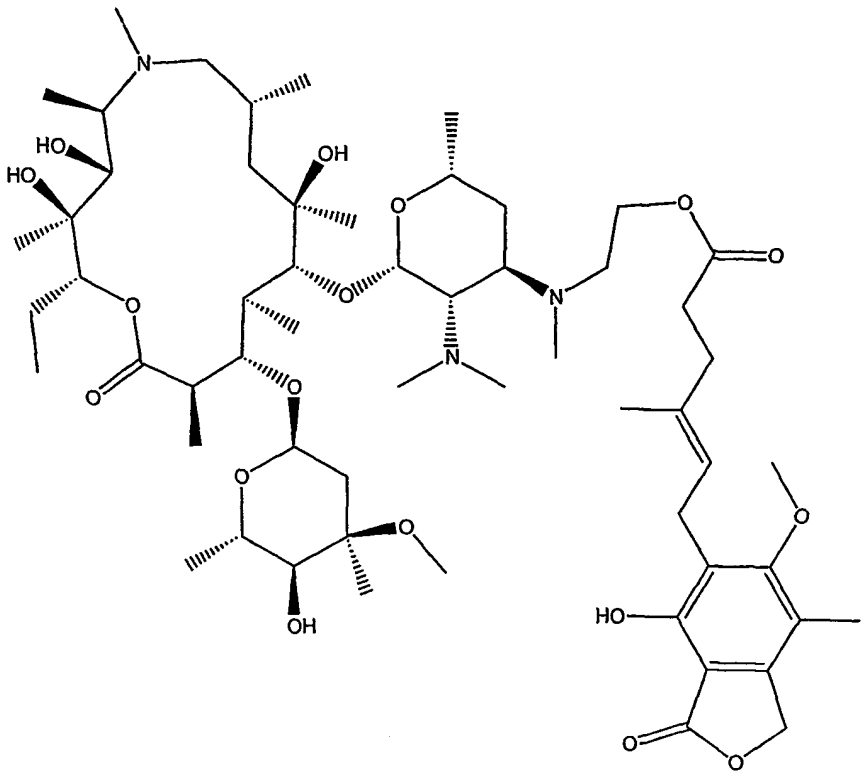
To a solution of mycophenolic acid ethyl ester (175mg, 0.5mmol) in chloroform (1 ml) is added ethyldiisopropylamine (85µL, 0.5 mmol). After stirring for 1 min Compound 70 (425mg, 0.5mmol) is added under nitrogen at 0-4°C.and afterwards chlor-*N,N*,2-trimethylpropenamine (1mL; 0.5mmol; 0.5mmol/mL solution in chloroform) is added drop-wise. The mixture is stirred at 0-4°C for 0.5 h and 12 h at room temperature. The mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1, affording 147 mg (25%) of a colorless solid.

Compound 71



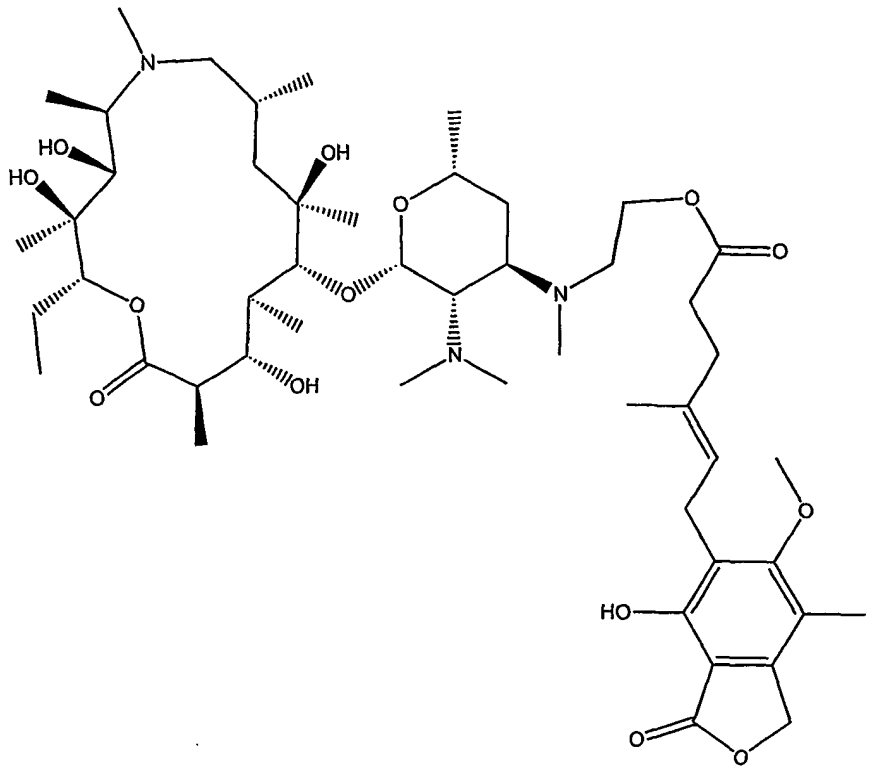
To mycophenolic acid (0.50g; 1.5mmol) and carbonyldiimidazole (0.25g; 1.5mmol), dissolved in methylene chloride (2mL) is added after 1 minute stirring at 0-4°C a solution of Compound **72**(0.27g, 0.5mmol) in 1 ml of dichloromethane. After stirring for 30min at 0-4°C the mixture is stirred for 12 h at room temperature. The mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1, affording 98 mg (23%) of a colorless solid.

Compound 73



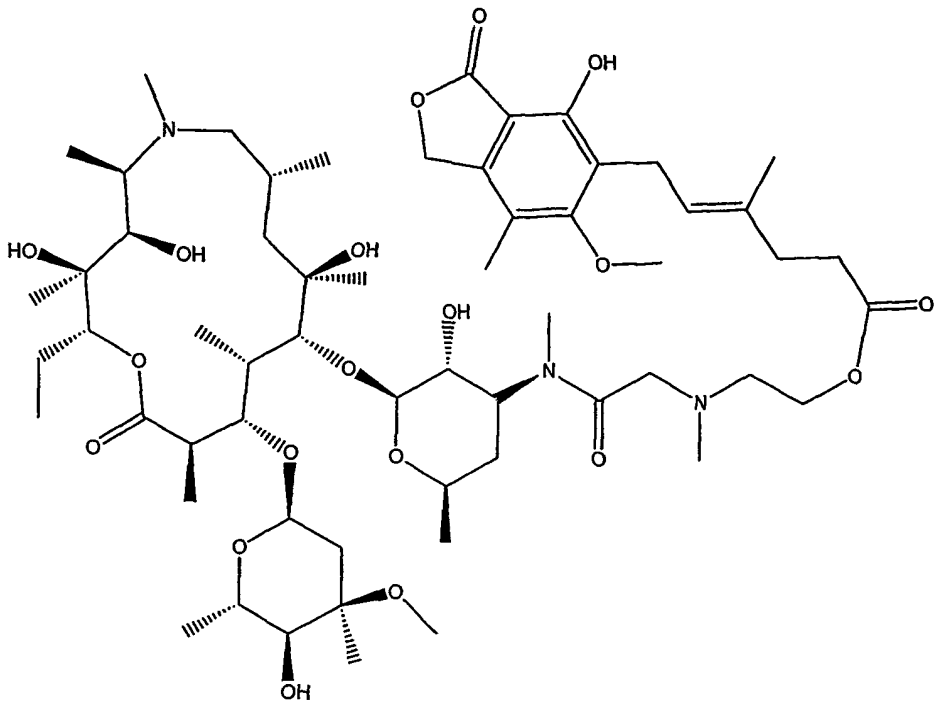
Mycophenolic acid (0.50 g; 1.5 mmol) is suspended in 3 ml of dichloromethane and treated with carbonyldiimidazole (0.25g; 1.5mmol). After 10 min a solution of Compound 44 (0.38g; 0.5mmol) in dichloromethane is added. After 30min at 0 °C the mixture is stirred for 12 h at room temperature. The mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1, affording 126 mg (22%) of a colorless foam.

COMPOUND 74



A solution of Compound 73 in 6 M HCl (20 ml) is kept at ambient temperature for 15 min and then extracted 5 ml of ethyl acetate. The organic phase is discarded and the aqueous phase neutralized with potassium carbonate and extracted with methylene chloride. The organic phase is dried (Na2SO4) and concentrated in vacuum to yield 400 mg (84%) of a colorless foam.

Compound 75



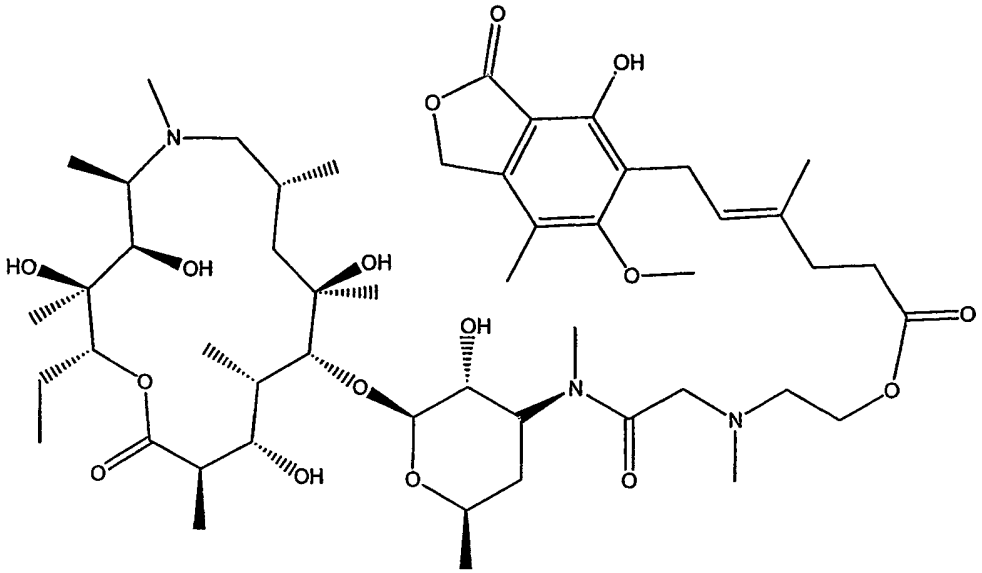
A solution of 1.1 g (1.5 mmol) of Compound 43 in 5 ml of dichloromethane was combined with 415 mg (2.25 mmol) of iodoacetic acid and 450 mg (2.25 mmol) of DCC. After 2 h at ambient temperature the mixture was filtered and the resulting Compound **76** was used without purification or concentration.

A solution 720 mg of (0.8 mmol) of Compound 76 in 3 ml of dichloromethane, prepared as described above, is diluted with 20 ml of DMF and 0.1 ml (1.2 mmol) of N-methyl amino ethanol is added. The mixture is kept at ambient temperature for 24 h. The mixture is poured onto a solution of potassium carbonate in water and extracted with dichloromethane. The organic phase is washed with brine, dried (Na2SO4 and concentrated in vacuum. The residue is chromatographed on silica gel, elution with chloroform/isopropanol/methanolic ammonia 80:1:1 to yield 210 mg (31%) of Compound **77**, a colorless solid.

A suspension of mycophenolic acid (0.50g; 1.5mmol) in 8 ml of dichloromethane was treated with carbonyldiimidazole (0.25g; 1.5mmolat 0°C. After 10 min a solution of Compound 77 (0.40 g, 0.5 mmol) in 2 ml of dichloromethane was added. After stirring for 30min. at 0-4°C the mixture is stirred for 24 h at room

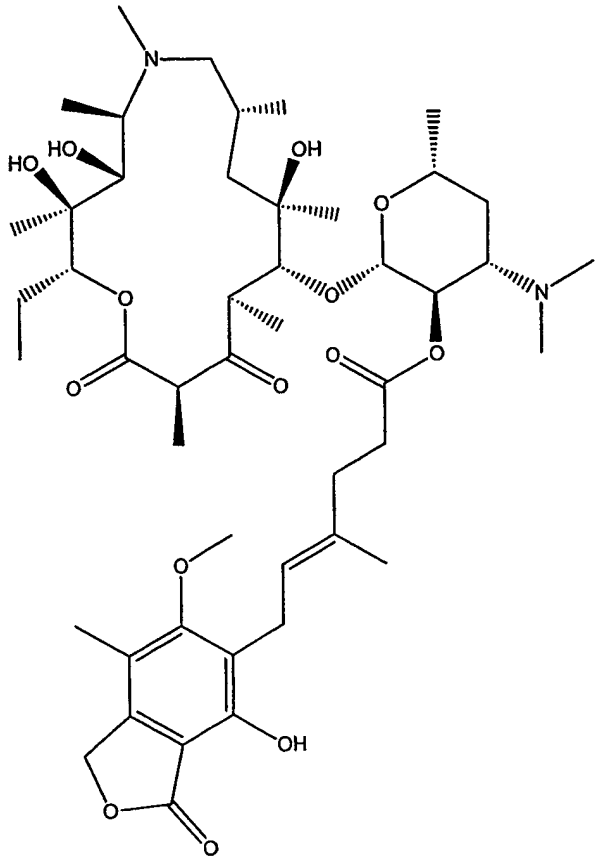
temperature. The mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1, affording 175mg (32%) of Compound 75.

Compound 78



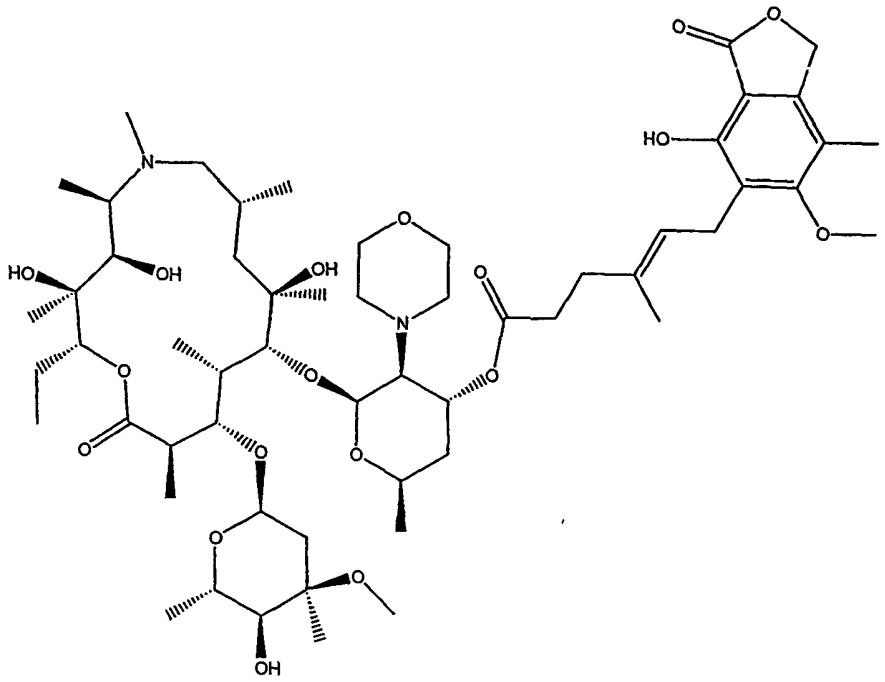
A solution of Compound 75 (550 mg, 0.5mmol) prepared as described before in 20 ml of 6 M HCl is kept at ambient temperature for 10 min and then extracted with diethylether. The organic phase is discarded and the aqueous phase neutralized with potassium carbonate and extracted with dichloromethane. The organic phase is washed with brine, dried (Na_2SO_4) and concentrated in vacuum to yield 420mg (89%) as a slightly yellowish foam.

Compound 79



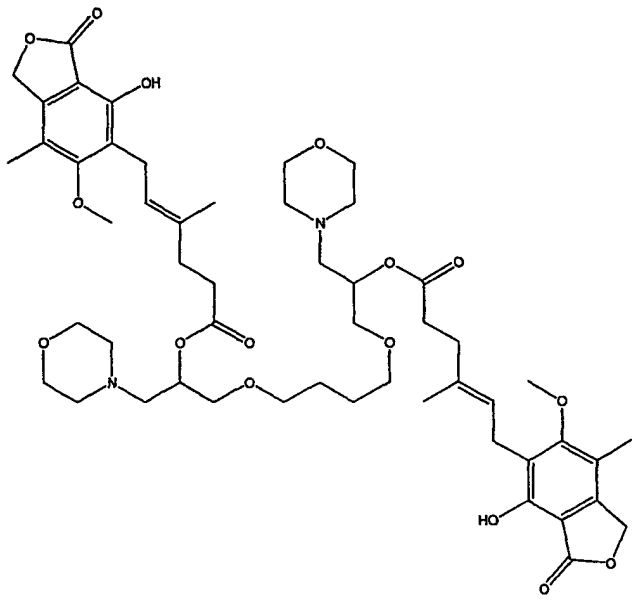
A suspension of mycophenolic acid (0.30g; 0.9mmol) in 8 ml of dichloromethane is treated with carbonyldiimidazole (0.15 g; 0.9 mmol) at 0°C. After 10 min a solution of Compound 40 (0.20 g, 0.3 mmol) in 2 ml of dichloromethane was added. After stirring for 30min. at 0-4°C the mixture is stirred for 24 h at room temperature. The mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1, affording 100mg (35%) of a colorless foam.

Compound 80



A mixture of 120 mg of Compound 48, 320 mg of mycophenolic acid and 300 mg of triphenyl phosphine is dissolved in 2 ml of THF under nitrogen. At 0°C 0.1 ml (0.5 mmol) diisopropyl azodicarboxylate is added in several portions within 4 h. After this time the mixture is allowed to warm to ambient temperature overnight. The reaction mixture is concentrated in vacuum and chromatographed on silica gel, elution with isopropanol.

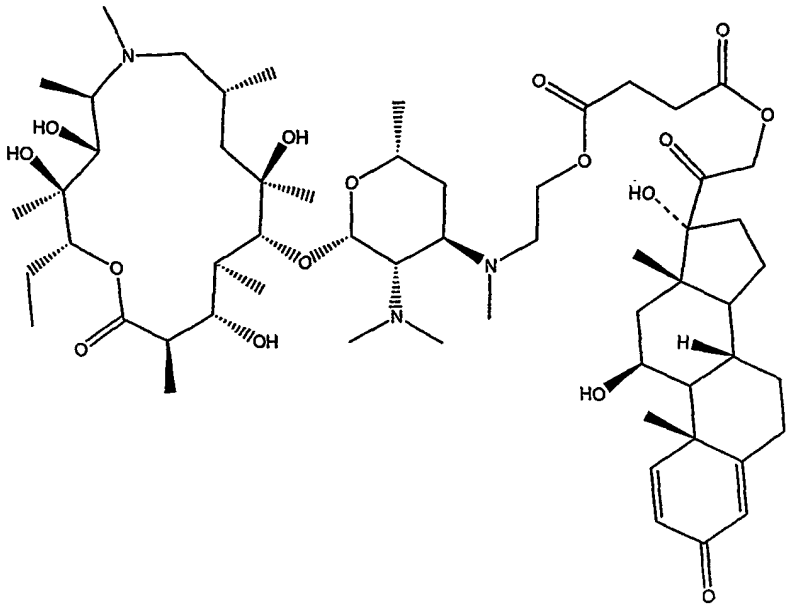
COMPOUND 81



To a solution of 188 mg of Compound 41, 400 mg of triphenylphosphine and 500 mg of mycophenolic acid in 3 ml of THF were added under nitrogen 0.3 ml of diisopropyl azodicarboxylate within 4 h at 0°C. The mixture was allowed to stir at 0°C for 3 h and was then allowed to warm to ambient temperature slowly. The reaction mixture was diluted with 70 ml of toluene and 30 ml of ethyl acetate and extracted repeatedly with ice-cold 0.5 M hydrogen chloride. The combined aqueous phases were extracted several times with a small quantity of toluene. The organic phases were discarded. The aqueous phase was treated with potassium carbonate until gas evolution had stopped and was then extracted with dichloromethane. Drying (Na_2SO_4) and concentration in vacuum yielded an oily residue that was purified by filtration through a short pad of silica gel (elution with ethyl acetate-triethyl amin) to yield 255 mg (52%) of a yellowish oil.

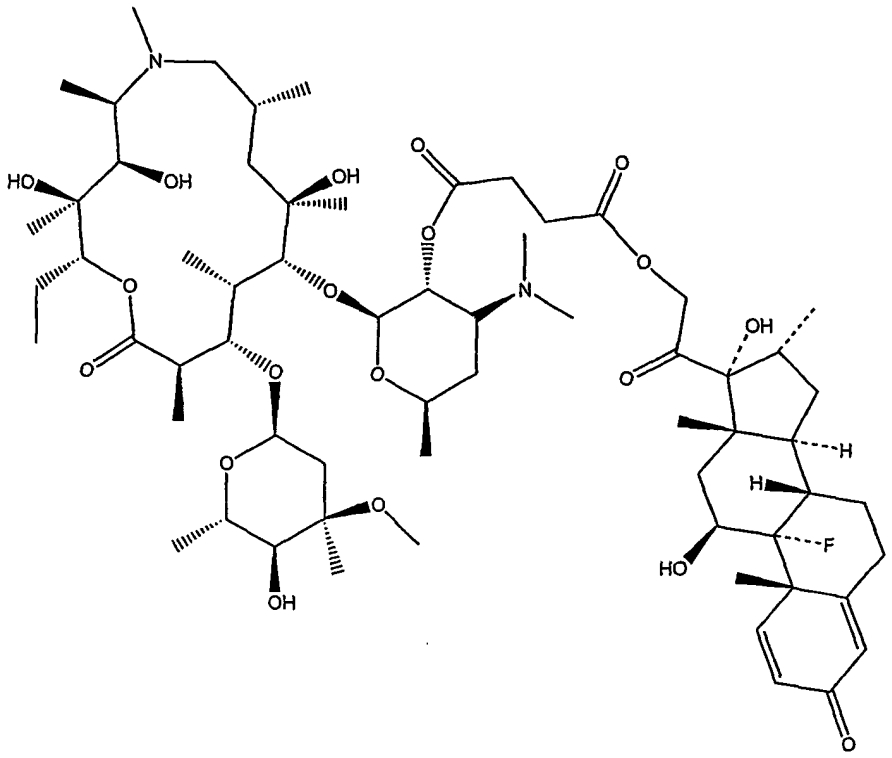
EXAMPLE 25: STEROID CONJUGATES

COMPOUND 82



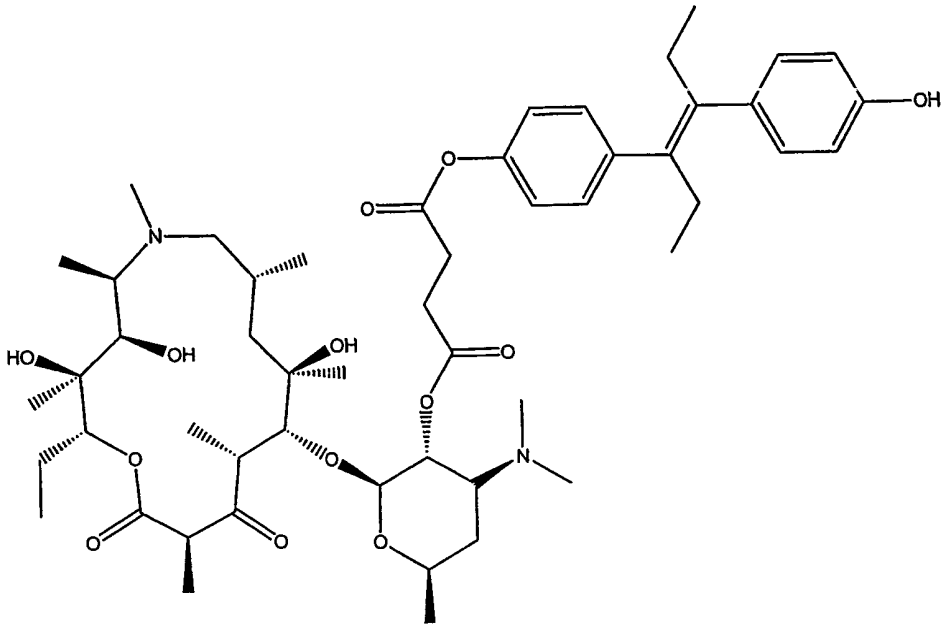
Prednisolone (180 mg, 0.5 mmol) is suspended in 3 ml of chloroform and 55 mg (0.55 mmol) of succinic anhydride is added. After 24 h at ambient temperature the mixture is cooled to 0°C and 325 mg of Compound 46 (0.5 mmol) is added followed by chlor-*N,N*,2-trimethylpropenamine (0.2 ml, 1.5 mmol) in several portions. The resulting solution is subjected to column chromatography on silica gel, elution with isopropanol to yield a white solid.

Compound 83



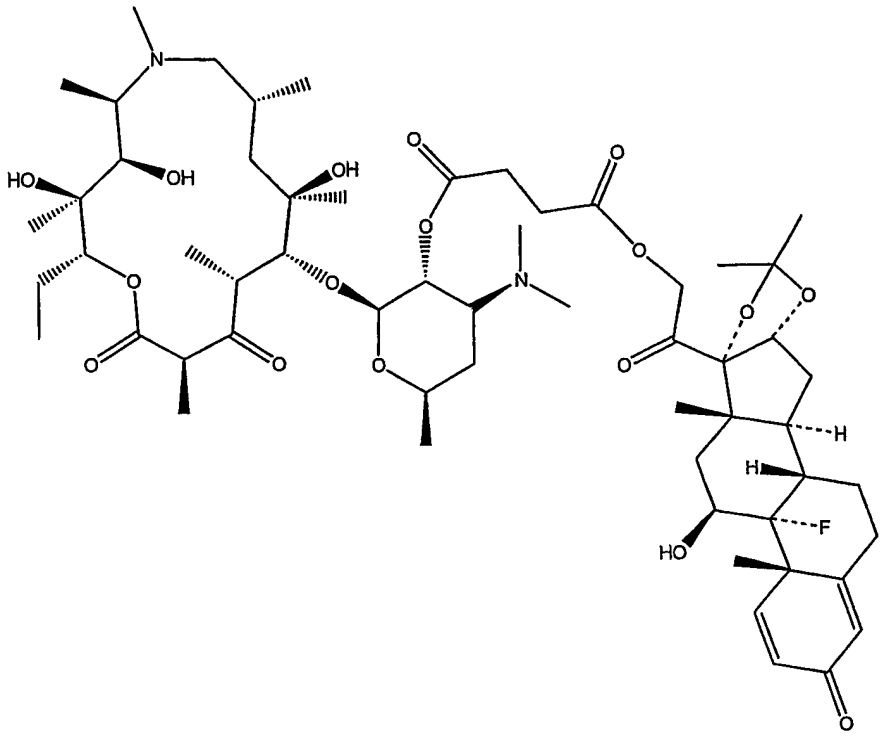
Dexamethasone (196 mg, 0.5 mmol) is suspended in 3 ml of chloroform and 55 mg (0.55 mmol) of succinic anhydride is added. After 24 h at ambient temperature 375 mg of Compound 43 (0.5 mmol) is added followed by chloro-*N,N*,2-trimethylpropenamine (0.2 ml, 1.5 mmol) in several portions. The resulting solution is after 1 h subjected to column chromatography on silica gel, elution with isopropanol to yield 198 mg (32%) of a white solid.

Compound 84



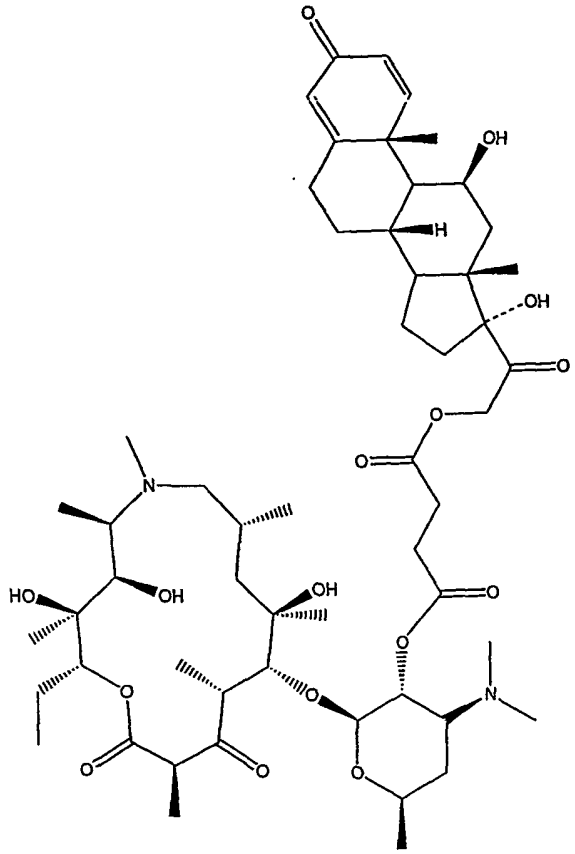
A solution of 295 mg (0.5 mmol) of Compound 40 in 4 ml of dichloromethane is treated with 55 mg (0.55 mmol) of succinic anhydride and the mixture stirred at ambient temperature overnight. To the reaction mixture diethylstilbestrol (174 mg, 0.5 mmol) and 0.15 ml of diisopropylethylamine is added followed by 0.133 ml of chloro-*N,N*,2-trimethylpropenamine (1.0 mmol) in several portions. After 1 h the reaction mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with ethyl acetate, changing to isopropanol, to yield 74 mg (16%) of a colorless solid.

Compound 85



A solution of 217 mg (0.5 mmol) of triamcinolone acetonide, 55 mg (0.55 mmol) of succinic anhydride in 3 ml of dichloromthane and 1 ml of pyridine is reacted 2 d at ambient temperature. After this period all volatiles are removed and the residue taken up in THF. To this mixture 100 mg (0.62 mmol) of carbonyldiimidazole is added under nitrogen, followed by 300 mg (0.51 mmol) of Compound 40. The mixture was heated to 50°C for 36 h. After cooling the mixture was concentrated in vacuum and the residue chromatographed on silica gel, elution with ethyl acetate, changing to isopropanol to yield 34 mg (6%) of a colorless solid.

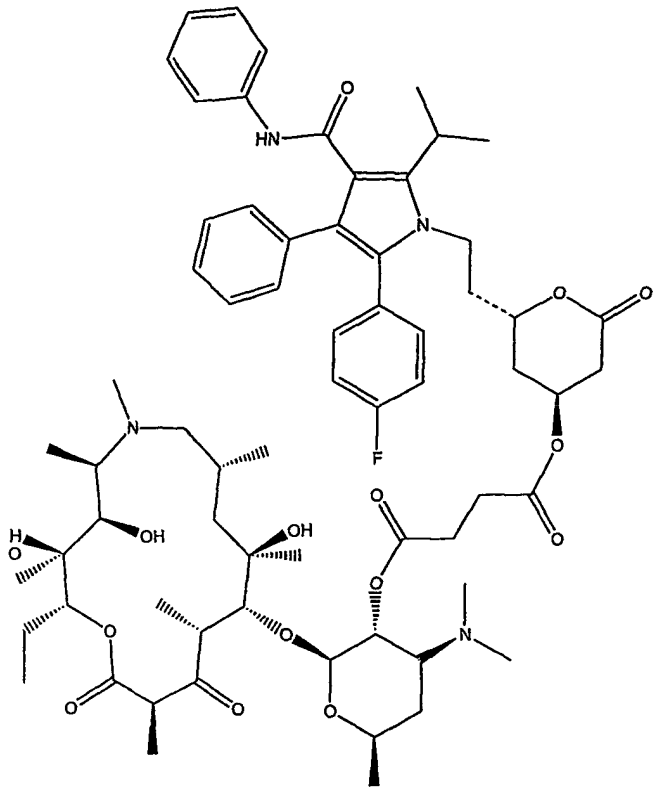
Compound 86



Prednisolone (180 mg, 0.5 mmol) is suspended in 3 ml of chloroform and 55 mg (0.55 mmol) of succinic anhydride is added. After 24 h at ambient temperature the mixture is cooled to 0°C and 295 mg of Compound 40 (0.5 mmol) is added followed by chlor-*N,N*,2-trimethylpropenamine (0.2 ml, 1.5 mmol) in several portions. The resulting solution is subjected to column chromatography on silica gel, elution with isopropanol to yield 165 mg (32%) of a white solid

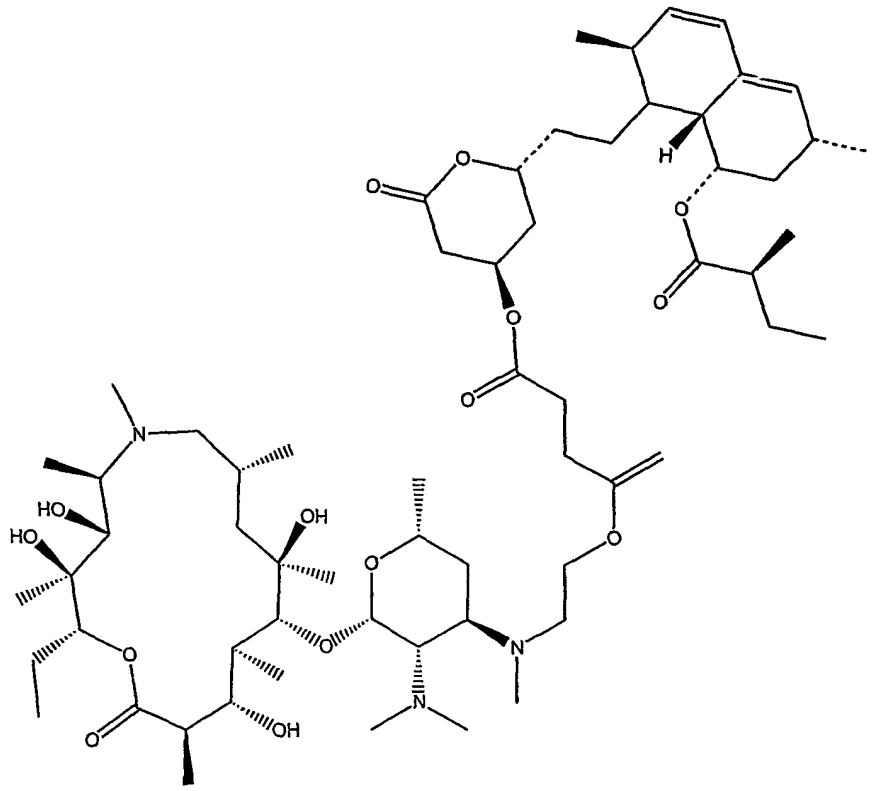
EXAMPLE 26: STATINS

COMPOUND 87



A solution of 560 mg (1 mmol) of atorvastatin in 10 ml of dichloromethane is treated with 2 ml of a 1 M solution of HCl in diethyl ether at ambient temperature for 12 h. The reaction mixture is washed with water and brine, dried (Na_2SO_4) and concentrated in vacuum. The residue is dissolved in 8 ml of chloroform and treated with 120 mg (1.2 mmol) of succinic anhydride and 123 mg (1.0 mmol) of DMAP under nitrogen. After 24 h at ambient temperature 194 mg (1.2 mmol) of carbonyldiimidazole is added, followed after 10 min by 700 mg (1.2 mmol) of Compound 40. The mixture is heated to 50°C for 36 h and then cooled, concentrated in vacuum and chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1 to yield 125 mg (10%) of a colorless solid.

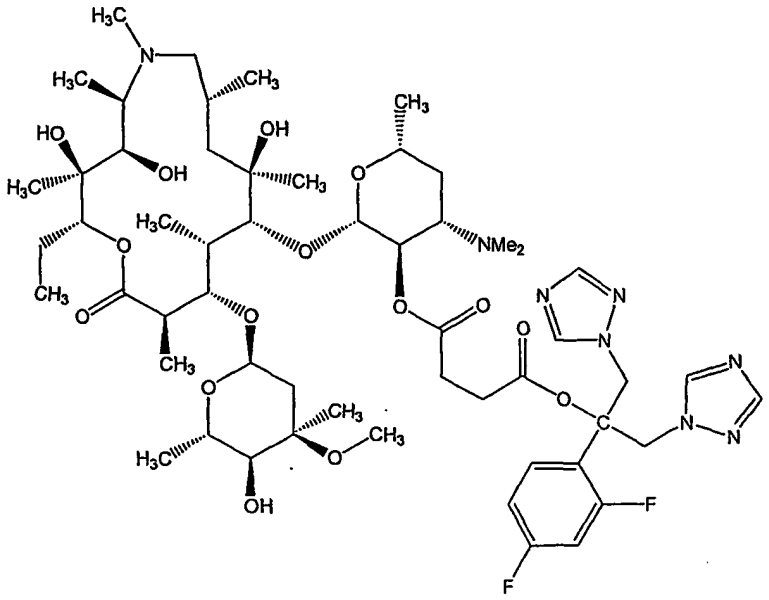
Compound 88



A solution of 25 mg (0.06 mmol) of lovastatin in 1 ml of dichloromethane was treated with 10 mg (0.1 mmol) of succinic anhydride under nitrogen. The mixture was kept at ambient temperature for 48 h and then 12 mg of carbonyldiimidazole is added followed after 10 min by 70 mg (0.11 mmol) of Compound 46. After stirring for 48 h at ambient temperature the mixture is concentrated in vacuum and the residue chromatographed on silica gel, elution with chloroform/2-propanol/ammonia 30:1:1 to yield 13 mg (19%) a white solid.

EXAMPLE 27: ANTIFUNGAL CONJUGATE

COMPOUND 89

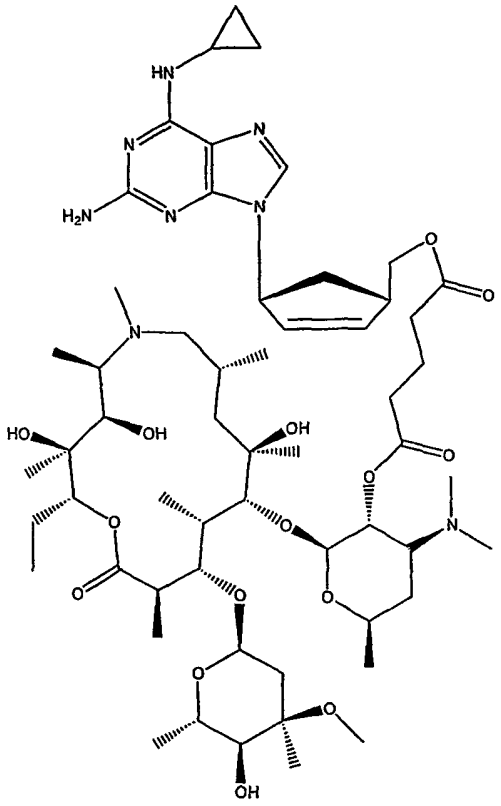


To a stirred solution of **Fluconazole** (0.67 g, 2.2 mmol) in anhydrous CH_2Cl_2 (20 ml) was added triethylamine (0.31 ml, 2.2 mmol) and succinic anhydride (0.22 g, 2.2 mmol). After stirring for 2 hours at ambient temperature N,N'-carbonyldiimidazole (0.37 g, 2.3 mmol) was added and stirred for another 2 hours. Subsequently Compound 43 (1.12 g, 1.5 mmol) was added and stirring continued overnight. Then the reaction mixture was diluted with CH_2Cl_2 (20 ml) und a saturated aqueous solution of sodium bicarbonate (30 ml). After separation, the organic layer was dried over Na_2SO_4, filtered and then concentrated under reduced pressure to furnish the crude product. Silica gel chromatography with THF-Hexane-NEt_3 (10:10:0.1) yielded Compound 89 as a white solid (0.20 g, 12%).

Alcohols

EXAMPLE 28: NUCLEOSIDES

Compound **90**



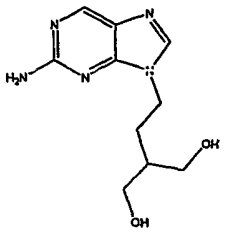
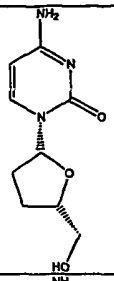
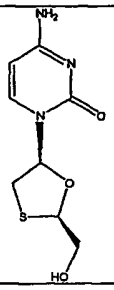
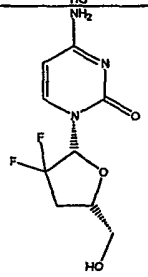
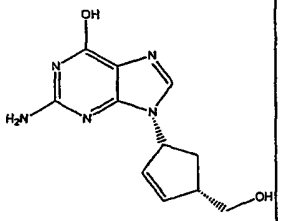
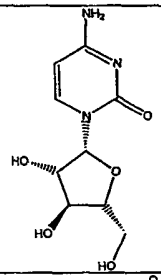
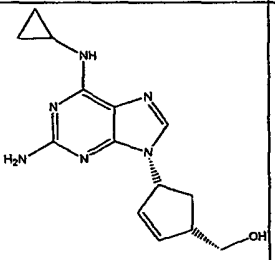
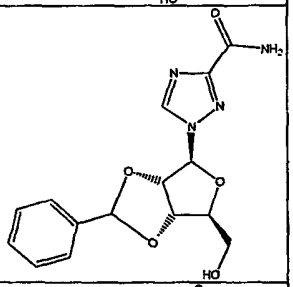
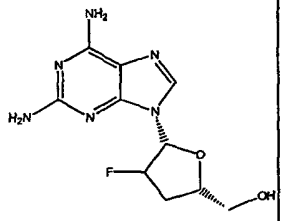
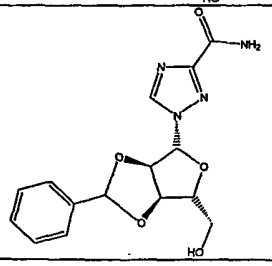
To a mixture of 800 mg glutaric acid (6 mmol, 6 eq.) and 500 mg CDI (3 mmol, 3 eq.) dissolved in 10 ml dry acetonitrile and stirred for 30 minutes at room temperature under argon, is added a solution of 750 mg Compound 43 (1 mmol) in the presence of a catalytic amount of DMAP dissolved in 5 ml acetonitrile. The reaction is refluxed overnight.

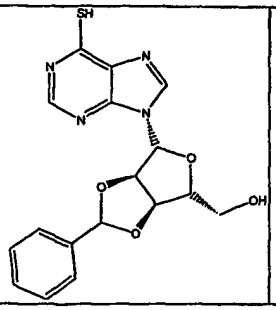
The solvent is removed *in vacuo*. The crude mixture is then purified by chromatography with chloroform/methanol/ammonia (94.5:10:0.5). The collected fractions yielded a white solid (340 mg, 45%). The expected Compound **91** is characterized by TLC (R_f = 0.4 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 863).

43 mg Compound 91 (0.05 mmol) and 15 mg Abacavir (0.05 mmol) are reacted in the presence of 12 mg DCC (0,06 mmol, 1.2 eq.). The mixture is dissolved in 1 ml of dry THF and stirred overnight at room temperature. The cloudy solution is filtered off and the solvent is removed *in vacuo*. The crude product is purified by chromatography. The collected fractions are concentrated to yield a white solid (20 mg, 40%). The expected Compound 90 is characterized by TLC ($R_f = 0.6$ in chloroform/methanol/ammonia (90:9:1)) and by MS (M+2H, 566).

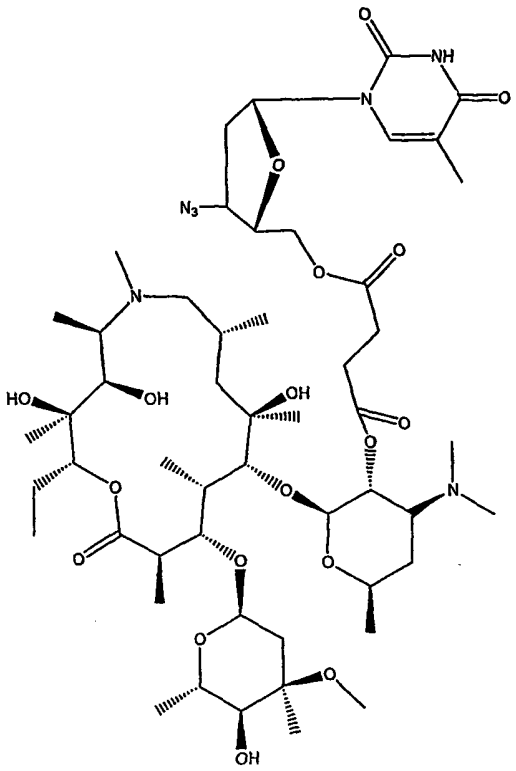
This protocol can be applied to other alcohols, some of which are listed in Table 3

Table 3 Representative class of alcohol compounds, which can be used in conjugation reactions.

Pencyclovir		Zalcitabine	
Lamivudine		Gemcitabine	
Carbovir		Cytarabine	
Abacavir		Levovirin – Benzylidene acetal	
Lodenosine		Ribavirin-Benzyliden acetal	

Mercaptopurine Riboside-benzylidenacetal			

Compound 92



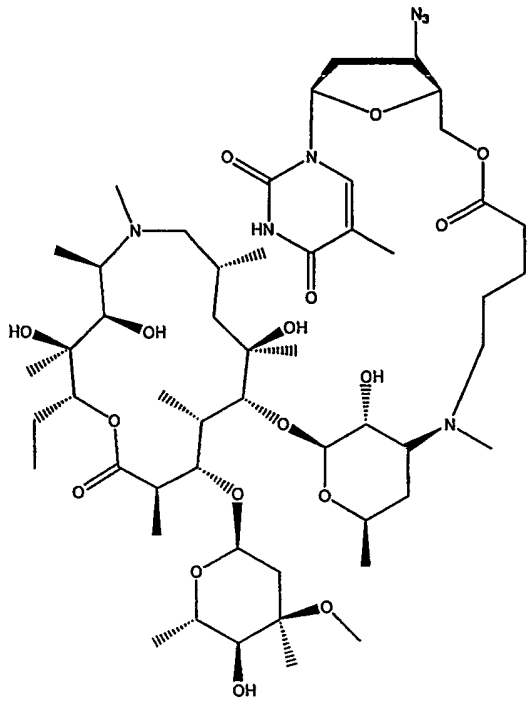
200 mg of Compound 43 (0.27 mmol) are treated with 30 mg succinic anhydride (0.3 mmol, 1.1 eq.) in 1 ml pyridine in the presence of a catalytic amount of DMAP. The reaction is stirred for 5 h at 40°C. After the completion of the reaction the product is separated by precipitation using hexane. The solution is decanted, and the recovered precipitate is washed several times with hexane to remove pyridine. The isolated compound is dried by high vacuum and yielded to a white solid (180 mg, 90%). The expected Compound **93** is characterized by MS ([M+H]+ = 850).

42 mg of Compound 93 (0.05 mmol) and 13 mg AZT (0.05 mmol) are coupled by using 11 mg DCC (0.055 mmol) in 0.5 ml of dry THF. The mixture is stirred overnight at room temperature. The cloudy solution is then filtered off to remove the urea.

The isolated crude product, obtained after removal of solvent, is purified by chromatography. The collected fractions yield after evaporation to a white solid (30 mg, 50%). The expected compound Compound 92 is characterized by TLC (R_f = 0.3 in chloroform/methanol/ammonia (90:9:1)) and by MS (M+2H, 549.7).

This protocol can be applied to other alcohols, some of which are listed in Table 3.

Compound 94



To a cloudy solution of 52 mg AZT (0.2 mmol), 43 mg 5-bromovaleric acid (0.24 mmol, 1.2 eq.), 106 mg BOP (0,24 mmol, 1.2 eq.), and a catalytic amount of DMAP in 1 ml dry THF are added 100 µl triethylamine (72 mg,700 µmol, 3 eq.). The clear solution is then stirred for 4 h at room temperature. After completion of reaction the crude mixture is purified by preparative TLC. Removal from the plate yields a yellowish oily solid (60 mg, 70%). The expected compound **95** is characterized by TLC (R_f = 0.7, chloroform/methanol/ammonia 90:9:1).

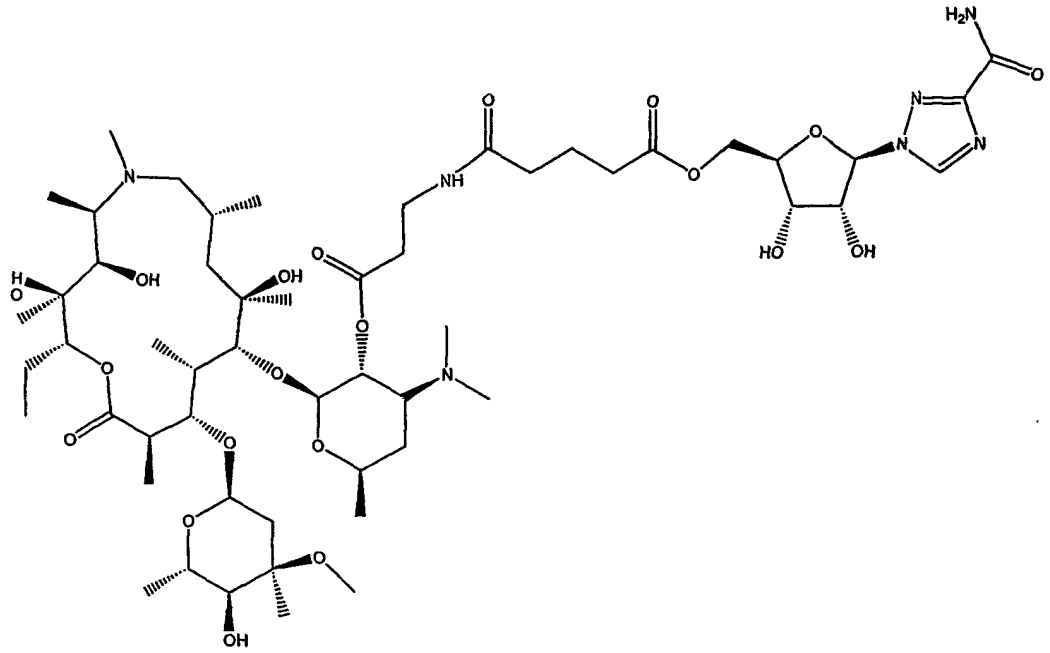
A solution of 6.0 g (8.0 mmol) of Compound 43 in 20 ml of THF is treated with 1.97 g (8.8 mmol) of N-iodosuccinic imide in several portions at 0°C. The mixture is kept at 10°C for 12 h and then poured into a solution of potassium carbonate in water and extracted with dichloromethane. The organic phase is dried (Na2SO4), concentrated in vacuum and the residue chromatographed on silica gel, elution with cyclohexane/ ethyl acetate/ isopropanol/ triethylamin 9:1:0.2:0.2 to yield 1.5 g (34%) of Compound **96**, a colorless solid.

To a cloudy solution of 8 mg Compound 95 (0.02 mmol) and 26 mg Compound 96 (0.035 mmol, 2 eq.) in acetonitrile (0.5 ml) is added am excess of

potassium carbonate. The reaction mixture is then set to 50°C for 48 h. The crude mixture is purified by chromatography to yield a yellowish solid (4.5 mg, 20%). The expected Compound 94 is characterized by TLC (R_f = 0.5 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 1113).

This protocol can be applied to other alcohols, some of which are listed in Table 3.

Compound 97



665 mg benzylidene-protected Ribavirin (2 mmol), 1.34 g glutaric acid (10 mmol, 5 eq.), 1 g CDI (6.2 mmol), and a catalytic amount of DMAP are suspended and heated in 20 ml of Chloroform for 3 h. The solvent is removed and the residue suspended in 1 M HCl, saturated with sodium chloride. The mixture is extracted twice with ethyl acetate, the organic layers are dried over sodium sulphate and evaporated to dryness. The residue is purified by chromatography to yield 760 mg (85%) of Compound **98**, characterized by TLC (Rf = 0.16 in THF/Hexane/Acetic acid 7:7:0.5) and MS ([M+H]+ = 447).

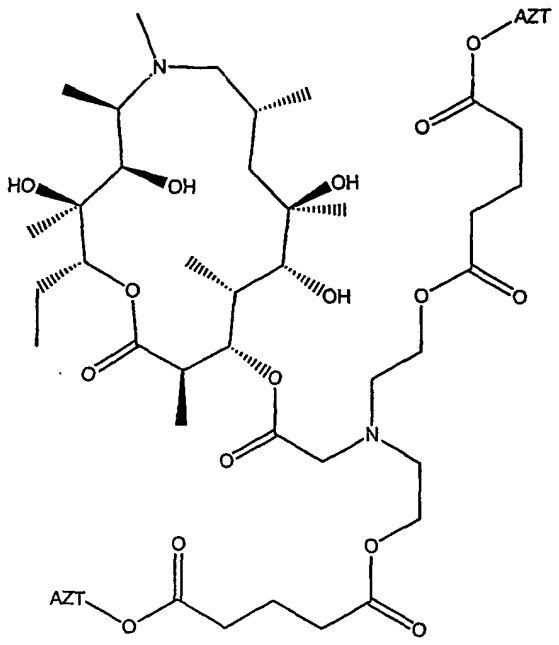
To a solution of 267 mg Z-ß-alanine (1.2 mmol, 1.2 eq.) and 190 mg CDI (1.2 mmol, 1.2 eq.) in 2 ml of dry THF, which had been stirred for 30 minutes at room temperature under argon, 749 mg Compound 43 are added (1 mmol). The mixture is then stirred overnight at 40°C. The clear and colorless solution is purified by flash chromatography. The collected fractions are concentrated to yield to a yellow solid (460 mg, 50%). The expected compound is characterized by TLC (R_f = 0.2 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 954.7). 450 mg of this compound (0.45 mmol) are dissolved in 5 ml of ethanol, to which an excess of

Pd/C is added under argon. The flask with hydrogen. The mixture is shaken gently overnight at room temperature. The Pd/C is removed passing the solution through a celite plug. The removal of solvent yielded a slighty black solid (280 mg, 76%), a mixture of Compound **99** and Compound 43. The expected Compound 99 is characterized by TLC (R_f = 0.2 in chloroform/methanol/ammonia (94.5:5:0.5)) and by MS ([M+H]+ = 890.5).

To a cloudy solution of 23 mg Compound 98 (0.05 mmol), and 41 mg free Compound 99. (0.05 mmol), 25 mg BOP (0,055 mmol, 1.1 eq.) and a catalytic amount of DMAP in 0.5 ml of dry THF are added 15 µl of triethylamine (11 mg, 0.11 mmol, 2 eq.). The clear solution is stirred overnight at room temperature. The mixture is purified by chromatography and yields 5 mg (10%) of a light yellowish solid. The expected Compound **100** is characterized by TLC (R_f = 0.25 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 1249).

5 mg of Compound 100 are dissolved in 5 ml 2-propanol and a tip of a spatula of Pd/C is added. The mixture is hydrogenated overnight. The catalyst is extracted with ethyl acetate and the extract purified by preparative TLC to yield 2.3 mg of the desired Compound 97, characterized by TLC (R_f = 0.45, chlororform/2-propanol/methanol/ammonia 25:3:1:1) and MS ([M+H]+ = 1161).

Compound **101**



900 mg of Compound 43 (1.2 mmol) are treated with 10 ml 12 N HCl in an iced-water bath overnight. The completed reaction is worked up by an extraction with chloroform. The aqueous phase is further neutralized at 0°C by addition of potassium hydroxide pellets to have a pH at 9-10. The orange basic aqueous phase is then extracted several times with chloroform. The combined organic layer is washed with brine and then dried over sodium sulphate. The crude product after evaporation of the solvent is purified by flash column chromatography to yield to a light yellowish solid (400 mg, 90%). The expected Compound **102** is characterized by TLC (R_f = 0.35 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 434).

300 mg of the Compound 102 (0.7 mmol), 190 mg iodoacetic acid (1 mmol, 1.5 eq.) and 210 mg DCC (1 mmol, 1.5 eq.) are dissolved in 5 ml of dry chloroform at 0°C under argon atmosphere under protection from light. The mixture is stirred overnight at room temperature. The yellowish cloudy solution is filtered off and the filtrate is concentrated under vacuum. Chromatography yields a fraction that contains mainly the monoacetylated product, Compound **103**, (yield: 175 mg, 50%) is characterized by TLC (R_f = 0.35 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 602).

To a solution of 150 mg of Compound 103 (0.25 mmol) in 2 ml of dry acetonitrile are added 50 µl of diethanolamine (0.5 mmol, 2 eq.). The mixture is stirred at room temperature for 1 h. After removal of the solvent the crude mixture is purified by flash chromatography. The collected fractions are concentrated under vacuum and yield a yellowish solid (60 mg, 40%). The expected compound 104 is characterized by TLC (R_f = 0.15 in chloroform/methanol/ammonia (90:9:1)) and MS ([M+H]+ = 579).

To a mixture of 800 mg glutaric acid (6 mmol, 6 eq.) and 500 mg CDI (3 mmol, 3 eq.) dissolved in 10 ml of dry acetonitrile, which is stirred for 30 minutes at room temperature under argon, are added 266 mg AZT (1 mmol) and a catalytic amount of DMAP. The cloudy reaction mixture is stirred overnight at 70°C. Chromatography yields a colorless sticky solid (120 mg, 35%). The expected compound 105 was characterized by TLC (R_f = 0.25 in chloroform/methanol/ammonia (90:9:1)) and MS ([M+H]+ = 381).

To a cloudy solution of 55 mg of Compound 105 (0.15 mmol, 3 eq.), and 29 mg of Compound 104 (0.05 mmol, 1 eq.), 38 mg BOP (0.18 mmol, 3.3 eq.) and a catalytic amount of DMAP in 0.5 ml of dry THF are added 30 µl of triethylamine (0.25 mmol, 4 eq.). The clear solution is then stirred overnight at room temperature. The mixture is purified by chromatography. The collected fractions yielded to a light yellowish solid (5 mg, 10%). The expected double acylated Compound 101 is characterized by TLC (R_f = 0.25 in chloroform/methanol/ammonia (90:9:1)) and by MS ([M+H]+ = 1306).

This protocol can be applied to other alcohols, some of which are listed in Table 3.

Abbreviations:

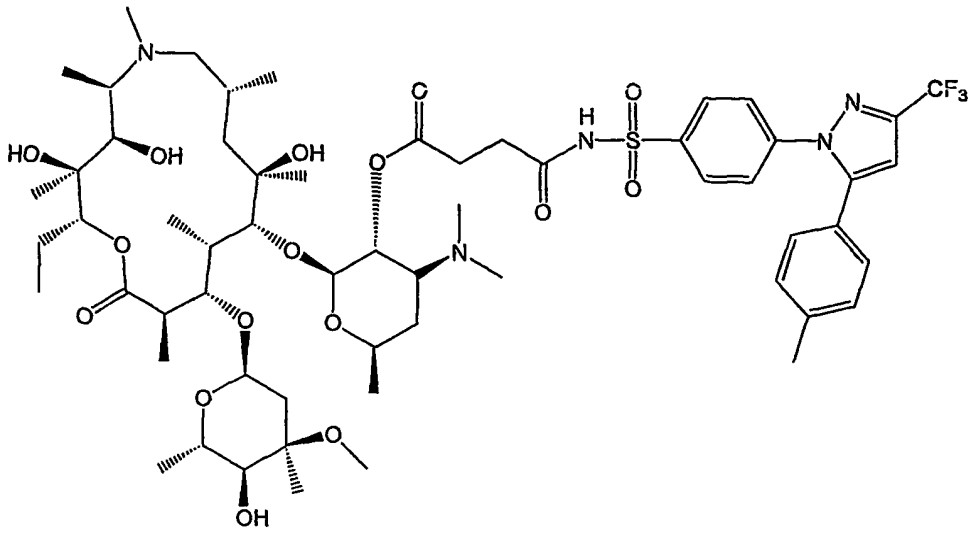
DMAP = 4-(N,N-dimethylamino)pyridine

BOP = (Benzotriazol-1-yloxy)-tris-(dimethylamino)-phosphonium-hexafluorophosphate

CDI = Carbonyldiimidazole

Z- = Benzyloxycarbonyl-

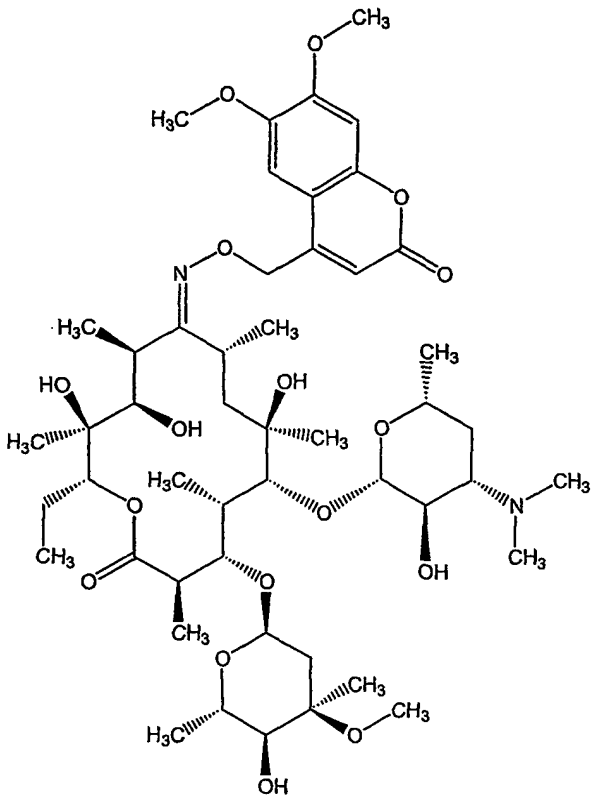
EXAMPLE 29: COMPOUND **106**



286 mg of Celecoxib (750µmol), 300 mg of succinic anhydride (3 mmol, 4 eq.), and 50 mg of DMAP are dissolved in 8 ml of dry acetonitrile. 420 µl (300µg, 3 mmol, 3 eq.) of triethylamine are added, and the reaction mixture is stirred overnight. 3 ml 1M aqueous sodium hydroxide and 5 ml of THF are added to remove excess succinic anhydride, the mixture is stirred for 2h. 180 µl of acetic acid (3.1 mmol) are added and the mixture is evaporated to dryness. The resulting oil is suspended in ethyl acetate. Diluted aqueous ammonia is added, and the aqueous phase is separated and evaporated until the gas evolution ceases. Concentrated HCl is added to obtain a yellow precipitate. The residue is dissolved in ethanol, evaporated to dryness and dried at 30°C/0.01mbar for 2 h. The yield of the resulting Compound **107** is 350 mg (93%), and can be used for the following step without further purification.

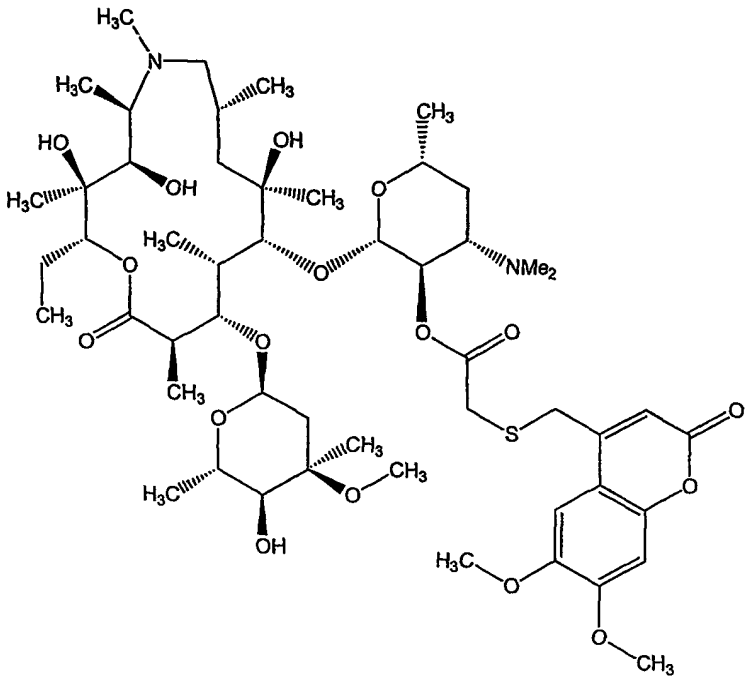
240 mg of Compound 107 (500µmol) are stirred together with 110 mg of CDI (650µmol, 1.3 eq.) in 8 ml of dry dichloromethane for 2 h. 300 mg (400µmol, 0.8 eq.) of Compound 43 are added and the mixture is stirred for an other 2 h. The mixture is subjected to chromatography after evaporation to yield 80 mg (16%) of the desired product, Compound 106 (MS: [M+H]+ = 1213).

EXAMPLE 30: COMPOUND 108



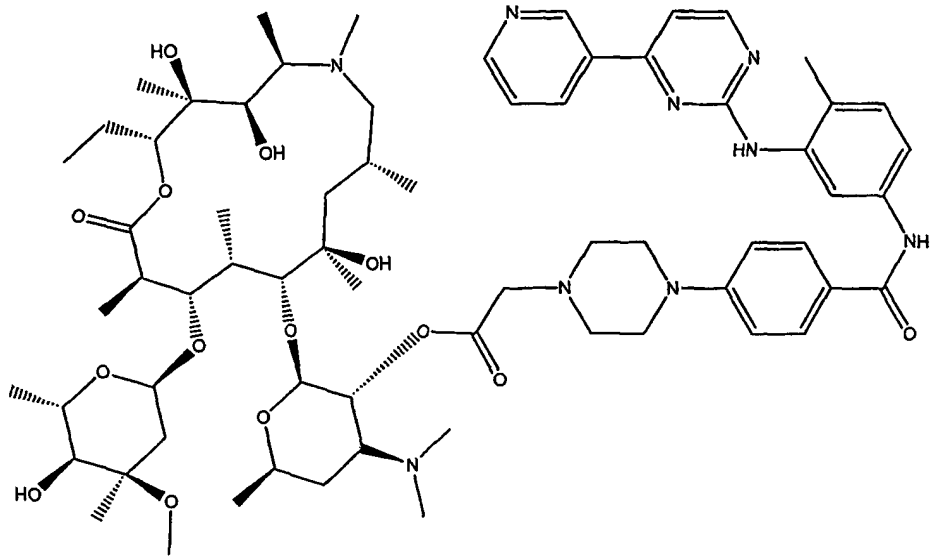
To a stirred solution of 1.12 g erythromycin A oxime (1.5 mmol) in 50 ml THF was added 1.5 ml 1 N potassium hydroxide solution (1.5 mmol) and 0.44 g 4-bromomethyl-6,7-dimethoxycoumarin (1.5 mmol). The reaction mixture was stirred at room temperature for 6 h and then filtered and treated with 44 µl of acetic acid. The solvent was removed under reduced pressure and the residue purified on silica gel, eluting with $CHCl_3$/MeOH/NH_4OH (6:1:0.1) to afford 0.4 g (28%) of Compound 108 a colorless foam. (MS: [M+H]+ = 968).

COMPOUND 109



To a stirred suspension of 0.46 g (6,7-dimethoxy-2-oxo-2H-chromen-4-yl methylsulfanyl)acetic acid (1.5 mmol) in 20 ml of dry CH_2Cl_2 are added 250 mg N,N′-carbonyldiimidazole (1.55 mmol). The reaction mixture is stirred for 2 h, then a solution of 1.0 g Compound 43 (1.3 mmol) in 10 ml of dry CH_2Cl_2 is added and stirring continued for 48 h. A saturated aqueous solution of sodium bicarbonate (30 ml) is added. The organic layer is dried over Na_2SO_4, filtered and then concentrated under reduced pressure to furnish the crude product. Chromatography affords the Compound 109 as a white foam (0.7 g, 52%). (MS: [M+H]+ = 1042).

EXAMPLE 31: COMPOUND 110



Imatinab may be selectively altered without compromising the interaction with the kinase and thus its biological activity (Schindler et al., Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Science 289, 1938-1942, 2000).

2.2g of 4-(4-Chlorocarbonyl-phenyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester and 1.15 g 4-Methyl-N3-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine (US 5,521,184) are reacted in 50 ml of dimethylformamide in the presence of 600 mg dimethylaniline for 24 h. The mixture is poured into 250 ml of ice-cold water. After filtration, the crude product is dried *in vacuo* and treated with a mixture of methanol and triethylamine (10:1). After evaporation of the solvent, the residue is subjected to chromatography to yield Compound **111**.

40 mg of Compound 111 are dissolved in 2 ml dry ethanol at 60°C and reacted with 31 mg of Compound 111 for 10h. The mixture is cooled to -21°C and filtered. The product, Compound 110, was obtained after recrystallisation. (MS: $[M+2H]^{2+}$ = 628).

Biological Methods

EXAMPLE 32: PROLIFERATION ASSAY

Assay to determine the *in vitro* rate of, for example, lymphocyte proliferation. Lymphocytes are purified out of ant coagulated (CPDA, citrate or heparin) mammalian blood using the Lymphoprep™ system (supplier). Purified cells are counted using a hemocytometer following Trypan Blue staining, and a cell concentration of 1 x 10^6 cells/ml established in RPMi 1640 medium with 10% FCS and antibiotics as required (all from Biochrome). Following the addition of a cell proliferation stimulant, for example phytohemagglutanin (Sigma) at, for example an end concentration of 5 µg/ml, the cells are incubated with different concentrations of the to be investigated compound in 100 µl end volume in a 96-well microtiter plate in an incubator (37°C, 5% CO_2, 95% humidity) for 72h. Cell proliferation is quantified following BrdU incorporation for 16 h by ELISA and subsequent colorimetric development (Cell Proliferation ELISA BrdU (colorimetric) kit from Roche Diagnostics). The IC_{50} (µM) values are then calculated, and used to compare compound efficacy.

To determine the influence of the T-L-C modification on *in vitro* cellular drug uptake and pharmacology, the above assay is additionally modified and an additional "wash" step included. In addition to running the assay for 72h with the compounds to be tested, the assay is also run for just 2h, then compound is washed away in three serial washing steps using 200 µl of medium at each step, and the cells subsequently incubated for a further 70h. The determined IC_{50} (µM) values following 2h and 72h incubation are compared and a ratio calculated (2h:72h). The lower the number, the better the uptake and drug release from the T-L-C in the cells (see results in Table 4 for examples), and improvement over mycophenolic acid.

Table 4 Proliferation assay results of T-L-C conjugates of mycophenolic acid

Conjugate	IC_{50} (μM) at 2h	IC_{50} (μM) at 72h	Ratio (2h:72h)
Mycophenolic acid	2.5	0.54	4.63
Mycophenolate mofetil	1.5	0.33	4.5
Compound 67	1.74	1.36	1.3
Compound 79	3.16	1.2	2.63
Compound 74	3.2	2.2	1.45
Compound 80	1.41	0.4	3.53
Compound 81	1.78	1.12	1.6
Compound 69	2.66	1.4	1.9

EXAMPLE 33: CELL-BASED IMDPH ASSAY WITH GUANOSINE RESCUE

Cytotoxicity assay

HeLa cells (DSMZ, ACC 57) and Jurkat cells (DSMZ, ACC 282) in exponential growth phase are exposed for 3 days to test compounds. The number of surviving cells is then determined by the Alamar Blue assay (Serotec Inc.). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. Specifically, the system incorporates an oxidation-reduction indicator that fluoresces in response to chemical reduction of the growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Continued growth maintains a reduced environment while inhibition of growth maintains an oxidized environment. Reduction from growth causes the Redox indicator to change from an oxidized to a reduced form. Fluorescence is monitored at 560 nm (Exc.) and 590 nm Em.

General procedure:

HeLa cells (1 $x10^3$) or JURKAT cells (1 $x10^3$) are plated in 100 µl MEM medium (with Earle's salt; Biochrom KG) containing 10% FBS, 2 mM L-glutamine, and non-essential animo acids in 96-well plates and incubated at 37°C and 5% CO_2 atmosphere. After 24 hours, the test compounds are added over a concentration range and the cells incubated for a further 48 hours. Alamar Blue reagent (20 µl) is added to each well, and the cultures incubated for a further 4 to 6 hours. The fluorescence is then measured as described above and the LD_{50} is determined based on a sigmoidal dose response regression. In order to determine the toxicity of T-L-C conjugates of mycophenolic acid not due to the inhibition of IMPDH, excess guanosine is added into the culture medium to a final concentration of 50 µM. Any toxicity still detected can then be ascribed either to other biological effects of the of T-L-C conjugate of mycophenolic acid, or is due to the very high intracellular concentration of mycophenolic acid, following concentrative uptake into the cell.

Cytotoxicity assay with fresh PBMNCs

The cytotoxicity of T-L-C conjugates of mycophenolic acid can be demonstrated directly on freshly isolated mammalian PBMNCs. The cells are

prepared as described in Example 29, and the level of cytotoxicity determined by the Alamar Blue assay, as described above. As described for both HeLa and JURKAT cells, guanosine can also be used here to ameliorate the effect of mycophenolic acid on the activity of IMPDH.

Results:

The toxicity of mycophenolic acid conjugates may be assessed most conveniently in a cell based system, preferably with a rapidly growing cell line such as HeLa or JURKAT. In normal culture conditions, mycophenolic acid has an IC_{50} of less than 2 uM, and its effect can be completely removed in the presence of 50 μM guanosine. For many of the T-L-C conjugates of mycophenolic acid, alleviation with guanosine is possible, but this is not always complete, which could for example be due to either to other biological effects of the of T-L-C conjugate of mycophenolic acid, or is due to the very high intracellular concentration of mycophenolic acid, following concentrative uptake into the cell.

EXAMPLE 35: Efficacy Testing of Immunosuppressive drugs using a Mouse Skin Transplant Model.

Skin transplant rejection is a strong immune response and serves as a very sensitive test of the immunosuppressive potential of drugs in organ transplantation and graft rejection. The mouse trunk skin transplant model was established using published methods (Billingham etal., 1954). Donor (Bl 10) trunk skin (approximately 8 x 8 mm) is removed and kept cold in saline before grafting on recipient Balb C mice. Male mice (n = 10) are dosed orally once a day from the day of transplant surgery (day 0) until the day of rejection. For each study, appropriate vehicle-treated control groups are run concurrently. Graft rejection is quantified as the number of days to reach R4 rejection (>75% of graft scabbed).

Results:

An example of results obtained with T-L-C conjugates of mycophenolic acid in the mouse skin transplant model are shown in FIG. 9. The mean rejection time for the vehicle, in this experiment saline, was 11.8 days, while the rejection time of the T-L-C conjugate Compound 67 was 13.5 days. Treatment with Compound 67 using dosage tapering (FIG. 10), resulted in a mean rejection time of 13.4 days.

EXAMPLE 36: Testing of antibiotic activity of drugs

Assay summary

The TC_{50} or MIC procedure for antibiotic sensitivity testing involves an antibiotic dilution assay, which can be performed in microtitre plates. A series of twofold dilutions of each antibiotic are made in the wells, and then all wells are inoculated with a standard amount of the same test organism. After incubation, growth in the presence of the various antibiotics is observed by measuring turbidity. Antibiotic sensitivity is expressed as the concentration of the antibiotic that inhibits 50% of the growth (TC_{50}). Alternatively it could be expressed as the highest dilution of antibiotic that completly inhibits growth (MIC).

Bacteria: *B. pumilus* and *E .coli* (DH5α)

Bacterial cultures are initiated from the plates for 2 to 3 weeks. After this time period bacteria are streaked out on new plates from the backups strored at -80°C. Due to the lack of resistance of the bacteria, new cultures are not to be initiated from an old plate or any liquid cultures derived from old plates.

Growth medium (GM)(per liter): 10 g Bacto-tryptone, 5 g Bacto-yeast extract, 6 g HEPES (25 mM), 5.4 g NaCl, pH 7.3

Compound stocks 10 or 100 mM in DMSO stored at -20°C.

Procedure

1. Grow *B.pumilus* from an LB agar plate in a flask (max. 10% volume) up to about 50 ml in growth medium (GM)
2. Dilute overnight suspension 1:10 in GM
3. Determine OD_{600} of diluted bacterial suspension
4. Dilute bacterial suspension in GM to an OD_{600} of 0.03 – 0.04. (6 ml / plate)
5. Add 200µl GM to the outer wells (Row A, Row H, Column 1, Column 12)
6. Add 100 µl GM to each well starting from C2, row 3.
7. Controls: Wells B2 – B4 growth control. Wells B6 – B8 blank. Row C growth inhibition control.

7.1. To wells B2 – B4 add: 96µl GM, 4µl DMSO, and 100µl bacterial suspension adjusted to an OD_{600} of 0.03 – 0.04.

7.2. To wells B6 - B8 add: 196 µl GM and 4 µl DMSO

7.3. Dilute a 10 mM COMPOUND 43 (positive control) stock to 800 µM (120 µl / plate) in GM. Add 100 µl of 800 µM COMPOUND 43 solution to well C2.

8. Samples

8.1. Dilute the 10 or 100 mM stock solutions to 800 µM (250 µl / plate) in GM.

8.2. Add 100 µl of 800 µM sample in duplicates to wells D2 / E2 resp. F2 / G2.

8.3. 2-fold serial dilution of all samples and Azithromycin

8.3.1. Rows C – G, Columns 2: Mix and transfer 100 µl from each row to Column 3, and continue until column 11. The remaining 100 µl out of column 11 are disposed.

9. Add 100 µl of bacterial suspension (OD_{600} 0.03 – 0.04) to each well from C2 – G11.

10. Incubate plates on shaker, 750 rpm, 37 °C, until the growth controls have reached an OD_{600} of 0.6 – 0.8 (approximately 6 – 8 h).

11. Determine OD_{600} on plate reader.

Table 5 TC_{50} values for representative compounds.

Compound	TC_{50} in E. coli (µM)
COMPOUND 43	2.3
COMPOUND 40	>50
COMPOUND 96	28
COMPOUND 53	>50
COMPOUND 45	>50

OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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Patents:

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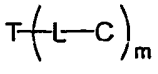
• JP05163293	514/252		

WHAT IS CLAIMED IS:

1. A compound of the following formula:



wherein

T is a transportophore,

L is a bond or a linker having a molecular weight up to 240 dalton,

C is a non-antibiotic therapeutic agent, and

m is 1, 2, 3, 4, 5, 6, 7, or 8,

in which the transportophore has an immune selectivity ratio of at least 2, the transportophore is covalently bonded to the non-antibiotic therapeutic agent via the bond or the linker, and the compound has an immune selectivity ratio of at least 2.

2. The compound of claim 1, wherein the transportophore is an amphiphilic molecule having a pKa value of 6.5 to 9.5.

3. The compound of claim 1, wherein the transportophore is a cyclic or heterocyclic molecule.

4. The compound of claim 3, wherein the cyclic or heterocyclic molecule has an attached sugar.

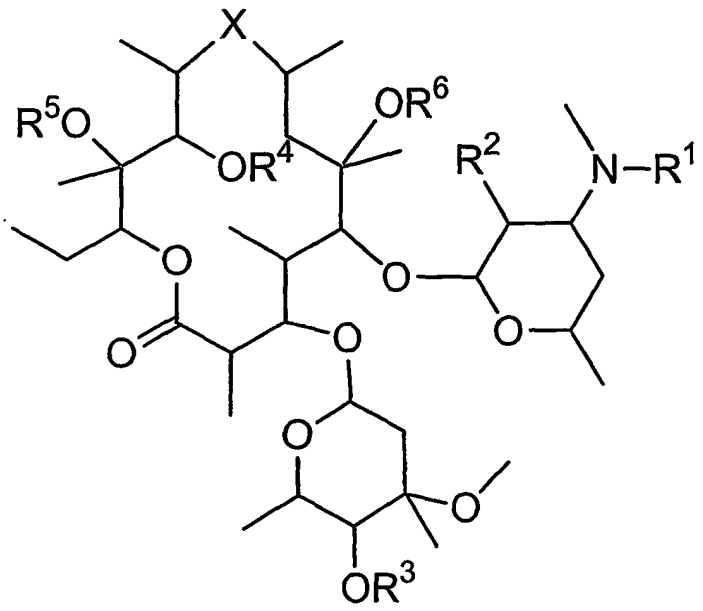
5. The compound of claim 3, wherein the cyclic or herterocyclic molecule is a macrolactone or macroether.

6. The compound of claim 5, wherein the macrolactone or macroether has an attached sugar.

7. The compound of claim 3, wherein the cyclic or herterocyclic molecule is a macrolide or ketolide having an amino sugar.

8. The compound of claim 7, wherein the cyclic or herterocyclic molecule is a macrolide having mono-, di-, or tri-basic groups.

9. The compound of claim 1, wherein the compound is



wherein

X = $N(R^7)$-CH_2

CH_2-$N(R^7)$

C(=O)

$C(=NOR^8)$

$CH(OR^9)$

$CH(NR^{10}R^{11})$

$C(=NR^{12})$

OC(=O)

C(=O)O

Y = independently linker

Z = C(=O)-

$CH(R^{16})$

R^1 = H

CH_3

$(C_2\text{-}C_{10})$alkyl

$(C_1\text{-}C_{10})$alkenyl

$(C_1\text{-}C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkenyl

$(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_5)$alkyl

$(C_2\text{-}C_9)$heteroaryl-$(C_1\text{-}C_5)$alkyl

$(C_1\text{-}C_4)$alkyliden-$NR^{18}R^{19}$

$Y\text{-}R^{13}$

$C(=O)\text{-}Y\text{-}R^{15}$

$C(=O)\text{-}R^{15}$

R^2 = H

(1′,2′-cis)-OH

(1′,2′-trans)-OH

(1′,2′-cis)-OR^{15}

(1′,2′-trans)-OR^{15}

(1′,2′-cis)-SH

(1′,2′-cis)-S-Y-R^{13}

or the R^1 and R^2 bearing atoms are connected via a -$OC(=O)CHR^{16}$- element

R^3 = H

$C(=O)\text{-}Y\text{-}R^{15}$

$C(=O)\text{-}R^{15}$

R^4 = H

$C(=O)\text{-}Y\text{-}R^{15}$

$C(=O)\text{-}R^{15}$

R^5 = H

or R^4, R^5 are connected by Z

R^6 = H

CH_3

R^7 = H

CH_3

$Y\text{-}R^{13}$

$C(=O)\text{-}Y\text{-}R^{15}$

$C(=O)\text{-}R^{15}$

$R^8 =$ H

$Y\text{-}R^{13}$

R^{13}

$C(=O)\text{-}R^{17}$

$(C_1\text{-}C_{10})$alkyl

$(C_1\text{-}C_{10})$alkenyl

$(C_1\text{-}C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkenyl

$(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_5)$alkyl

$(C_2\text{-}C_9)$heteroaryl-$(C_1\text{-}C_5)$alkyl

$(C_1\text{-}C_4)$alkyliden-$NR^{18}R^{19}$

wherein alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $-NR^{18}R^{19}$, $R^{18}C(=O)$-, $R^{18}C(=O)O$-, $R^{18}OC(=O)O$-, $R^{18}NHC(=O)$-, $R^{18}C(=O)NH$-, $R^{18}R^{19}NC(=O)$-and $R^{18}OC(=O)$-

$R^9 =$ H

$(C_1\text{-}C_{10})$alkyl

$(C_1\text{-}C_{10})$alkenyl

$(C_1\text{-}C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkenyl

$(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_5)$alkyl

$(C_2\text{-}C_9)$heteroaryl-$(C_1\text{-}C_5)$alkyl

wherein alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl,

$(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $-NR^{18}R^{19}$, $R^{18}C(=O)-$, $R^{18}C(=O)O-$, $R^{18}OC(=O)O-$, $R^{18}NHC(=O)-$, $R^{18}C(=O)NH-$, $R^{18}R^{19}NC(=O)-$and $R^{18}OC(=O)-$

R^{10}, R^{11}= independently H

$(C_1$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkenyl

$(C_6$-$C_{10})$aryl-$(C_1$-$C_5)$alkyl

$(C_2$-$C_9)$heteroaryl-$(C_1$-$C_5)$alkyl

$(C_1$-$C_4)$alkyliden-$NR^{18}R^{19}$

or R^{10} = H and R^{11} = $-Y-R^{13}$

$C(=O)-Y-R^{15}$, $-C(=O)-R^{15}$

R^{12}= H

$(C_1$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkenyl

$(C_6$-$C_{10})$aryl-$(C_1$-$C_5)$alkyl

$(C_2$-$C_9)$heteroaryl-$(C_1$-$C_5)$alkyl

$(C_1$-$C_4)$alkyliden-$NR^{18}R^{19}$

$Y-R^{13}$

R^{13}= independently, therapeutic agent

R^{15}= independently, therapeutic agent

R^{16}= independently, H

CH_3

$(C_2$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)alkoxy]alkenyl$

$(C_6\text{-}C_{10})aryl\text{-}(C_1\text{-}C_5)alkyl$

$(C_2\text{-}C_9)heteroaryl\text{-}(C_1\text{-}C_5)alkyl$

$(C_1\text{-}C_4)alkyliden\text{-}NR^{18}R^{19}$

$Y\text{-}R^{13}$,

R^{17}= $O\text{-}R^{20}\text{-}aryl$

optionally substituted by –X'-Y- therapeutic agent, X'-therapeutic agent wherein X' is S, O, or NH

R^{18}, R^{19}= independently H

$(C_1\text{-}C_{10})alkyl$

$(C_1\text{-}C_{10})alkenyl$

$(C_1\text{-}C_{10})alkynyl$

$(C_1\text{-}C_8)[(C_1\text{-}C_4)alkoxy]alkyl$

$(C_1\text{-}C_8)[(C_1\text{-}C_4)alkoxy]alkenyl$

$(C_6\text{-}C_{10})aryl\text{-}(C_1\text{-}C_5)alkyl$

$(C_2\text{-}C_9)heteroaryl\text{-}(C_1\text{-}C_5)alkyl$

R^{20} = independently,

Halogen

$(C_1\text{-}C_3)alkyl$

NO_2

CN

OCH_3

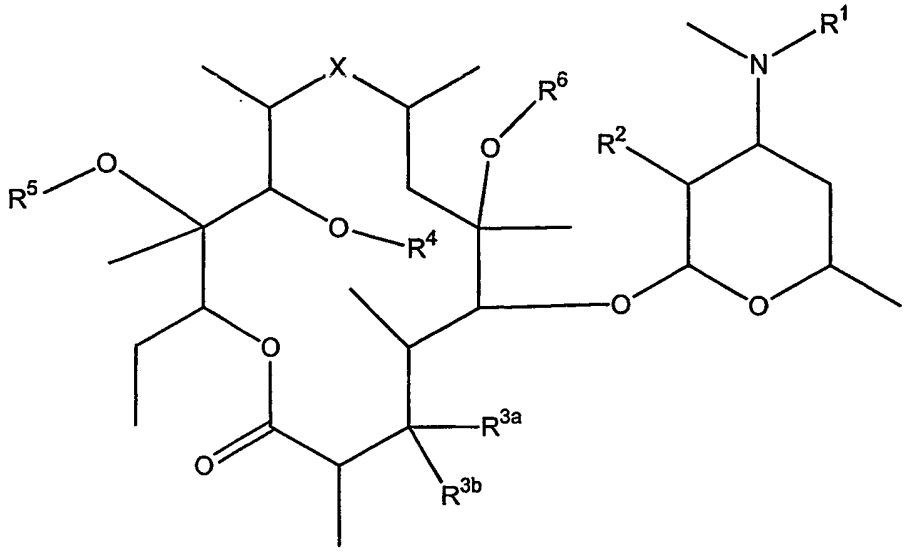
$N(CH_3)_2$

N_3

SH

$S(C_1\text{-}C_4)alkyl$.

10. The compound of claim1, wherein the compound is



wherein:

X = $N(R^7)$-CH_2

CH_2-$N(R^7)$

C(=O)

$C(=NOR^8)$

$CH(OR^9)$

$CH(NR^{10}R^{11})$

$C(=NR^{12})$

OC(=O)

C(=O)O

Y = independently, linker

Z = C(=O)-

$CH(R^{16})$-

R^1 = H

CH_3

$(C_2$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)alkoxy]alkyl$

$(C_1\text{-}C_8)[(C_1\text{-}C_4)alkoxy]alkenyl$

$(C_6\text{-}C_{10})aryl\text{-}(C_1\text{-}C_5)alkyl$

$(C_2\text{-}C_9)heteroaryl\text{-}(C_1\text{-}C_5)alkyl$

$(C_1\text{-}C_4)alkyliden\text{-}NR^{18}R^{19}$

$Y\text{-}R^{13}$

$C(=O)\text{-}Y\text{-}R^{15}$

$C(=O)\text{-}R^{15}$

$S(=O)_k(C_1\text{-}C_{10})alkyl$

$S(=O)_k(C_1\text{-}C_{10})alkenyl$

$S(=O)_k(C_1\text{-}C_{10})alkynyl$

$S(=O)_k(C6\text{-}C_{10})aryl$

$S(=O)_k(C_2\text{-}C_9)heteroaryl$

$S(=O)_k\text{-}Y\text{-}R^{15}$

$S(=O)_k\text{-}R^{15}$

wherein k is 0, 1 or 2 and alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl can optionally be substituted by one to three halogen, cyano, hydroxy, $(C_1\text{-}C_4)$alkyloxy, nitro, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $NR^{18}R^{19}$, $R^{18}C(=O)\text{-}$, $R^{18}C(=O)O\text{-}$, $R^{18}OC(=O)\text{-}$, $R^{18}C(=O)NH\text{-}$, $R^{18}NHC(=O)\text{-}$, $R^{18}R^{19}NC(=O)\text{-}$ or $R^{18}OC(=O)\text{-}O\text{-}$

R^2 = H

(1′,2′-cis)-OH

(1′,2′-trans)-OH

(1′,2′-cis)-OR^{15}

(1′,2′-trans)-OR^{15}

(1′,2′-cis)-SH

(1′,2′-cis)-S-Y-R^{13}

or the R^1 and R^2 bearing atoms are connected via a $-OC(=O)CHR^{16}-$ element

R^{3a}, R^{3b} = independently H

R^1

OH

OR^{11}

$NR^{10}R^{11}$

or $R^{3a} = R^{3b} = (=O)$,

$(=NR^{1})$

$O(CH_2)_kO$- wherein k is 2 or 3

$R^4 =$ H

$C(=O)$-Y-R^{15}

$C(=O)$-R^{15}

$R^5 =$ H

or R^4, R^5 are connected by -Z-

$R^6 =$ H

CH_3

$R^7 =$ H

CH_3

Y-R^{13}

$C(=O)$-Y-R^{15}

$C(=O)$-R^{15}

$R^8 =$ H

Y-R^{13}

$C(=O)$-R^{17}

$R^9 =$ H

$(C_1$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkenyl

$(C_6$-$C_{10})$aryl-$(C_1$-$C_5)$alkyl

$(C_2$-$C_9)$heteroaryl-$(C_1$-$C_5)$alkyl

R^{10}, R^{11}= independently H

$(C_1$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_3$-$C_{10})$cycloalkyl

$(C_1$-$C_9)$heterocycloalkyl

$(C_6$-$C_{10})$aryl

$(C_2$-$C_9)$heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl are optionally substituted by one to three halogen, cyano, hydroxy, $(C_1$-$C_4)$alkyloxy, nitro, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $NR^{18}R^{19}$, $R^{18}C(=O)$-, $R^{18}C(=O)O$-, $R^{18}OC(=O)$-, $R^{18}C(=O)NH$-, $R^{18}NHC(=O)$-, $R^{18}R^{19}NC(=O)$- or $R^{18}OC(=O)$-O-

or R^{10} = H and

R^{11} = Y-R^{13}

$C(=O)$-Y-R^{15}

$C(=O)$-R^{15}

$S(=O)_k(C_1$-$C_{10})$alkyl

$S(=O)_k(C_1$-$C_{10})$alkenyl

$S(=O)_k(C_1$-$C_{10})$alkynyl

$S(=O)_k(C6$-$C_{10})$aryl

$S(=O)_k(C_2$-$C_9)$heteroaryl

$S(=O)_k$-Y-R^{15}

$S(=O)_k$-R^{15}

wherein k is 0, 1 or 2 and alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl can be substituted as defined above.

R^{12}= H

$(C_1$-$C_{10})$alkyl

$(C_1$-$C_{10})$alkenyl

$(C_1$-$C_{10})$alkynyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkyl

$(C_1$-$C_8)[(C_1$-$C_4)$alkoxy]alkenyl

$(C_6$-$C_{10})$aryl-$(C_1$-$C_5)$alkyl

$(C_2$-$C_9)$heteroaryl-$(C_1$-$C_5)$alkyl

$(C_1$-$C_4)$alkyliden-$NR^{18}R^{19}$

$Y\text{-}R^{13}$

R^{13}= independently, therapeutic agent

R^{15}= independently, therapeutic agent

R^{16}= independently, H

CH_3

$(C_2\text{-}C_{10})$alkyl

$(C_1\text{-}C_{10})$alkenyl

$(C_1\text{-}C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkenyl

$(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_5)$alkyl

$(C_2\text{-}C_9)$heteroaryl-$(C_1\text{-}C_5)$alkyl

$(C_1\text{-}C_4)$alkyliden-$NR^{18}R^{19}$

$Y\text{-}R^{13}$

R^{17}= O-R^{20}-aryl

optionally substituted by –X'-Y- therapeutic agent, X'- therapeutic agent wherein X' is

S, O, NH

R^{18}, R^{19}= independently H

$(C_1\text{-}C_{10})$alkyl

$(C_1\text{-}C_{10})$alkenyl

$(C_1\text{-}C_{10})$alkynyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkyl

$(C_1\text{-}C_8)[(C_1\text{-}C_4)$alkoxy]alkenyl

$(C_6\text{-}C_{10})$aryl-$(C_1\text{-}C_5)$alkyl

$(C_2\text{-}C_9)$heteroaryl-$(C_1\text{-}C_5)$alkyl

R^{20} = independently,

Halogen

$(C_1\text{-}C_3)$alkyl

NO_2

CN

OCH_3

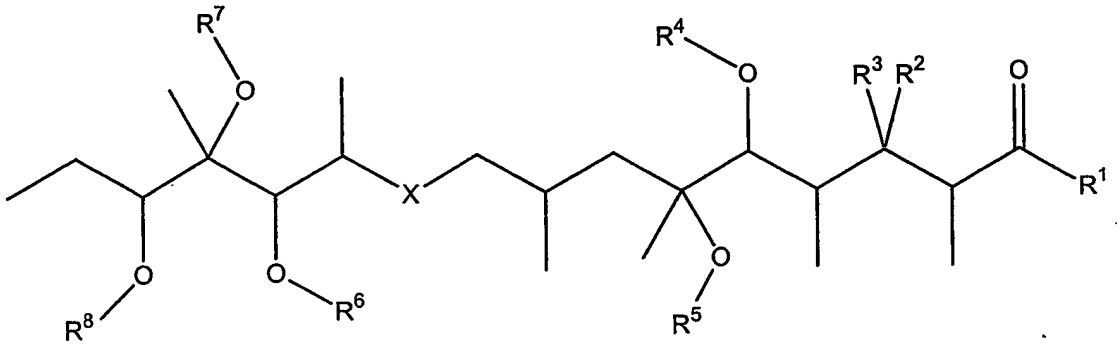
$N(CH_3)_2$

N_3

SH

$S(C_1\text{-}C_4)$alkyl.

11. The compound of claim 1, wherein the compound is



wherein

X = $N(R^9)\text{-}CH_2$

$CH_2\text{-}N(R^9)$

C(=O)

$C(=NOR^{10})$

$C(OR^{11})H$

$CH(NR^{12}R^{13})$

$C(=NR^{14})$

OC(=O)

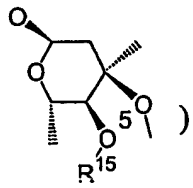
C(=O)O

Y = independently, linker

R^1 = OR^{17}

$NR^{17}R^{18}$,

or R^1 is connected to the oxygen bearing R^4 or R^5 forming a lactone or is connected to a suitable substituent in R^2 forming a lactone or lactam,

R^2 = O-2-cladinosyl ()

H

X', wherein X'= halogen

azido

nitro

cyano

OR^{17}

OR^{22}

$NR^{17}R^{18}$

SR^{17} (C_1-C_6)alkyl

(C_1-C_6)alkenyl

(C_1-C_6)alkynyl

(C_3-C_{10})cycloalkyl

(C_1-C_9)heterocycloalkyl

(C_6-C_{10})aryl

(C_1-C_9)heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, (C_1-C_4)alkyl, (C_1-C_4)alkenyl, (C_1-C_4)alkynyl, (C_3-C_7)cycloalkyl, (C_1-C_6)heterocycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_4)alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

R^3 = H

(C_1-C_6)alkyl

(C_1-C_6)alkenyl

(C_1-C_6)alkynyl

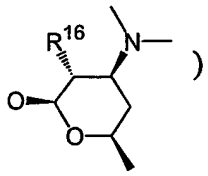
(C_3-C_{10})cycloalkyl

(C_1-C_9)heterocycloalkyl

(C_6-C_{10})aryl

$(C_1\text{-}C_9)$heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_4)$alkoxy, or $R^{20}R^{21}N$-

R^4 = O-2-desosaminyl ()

H

$C(=O)R^{17}$

Y- therapeutic agent

therapeutic agent

$S(=O)_2R^{17}$ providing R^{17} is not hydrogen

$C(=O)NR^{17}R^{18}$ $(C_1\text{-}C_6)$alkyl

$(C_1\text{-}C_6)$alkenyl

$(C_1\text{-}C_6)$alkynyl

$(C_3\text{-}C_{10})$cycloalkyl

$(C_1\text{-}C_9)$heterocycloalkyl

$(C_6\text{-}C_{10})$aryl

$(C_1\text{-}C_9)$heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

or R^4 is connected to a suitable R^2 containing a N or a O by -C(=O), $S(=O)_n$ wherein n = 1 or 2, $-CR^{20}R^{17}$-, CR^{20}(-Y- therapeutic agent)-, $-CR^{20}$(-therapeutic agent)- forming in dependence of R^2 a 6 or 7-membered ring,

R^5 = R^{20}

$C(=O)R^{20}$

or R^4, R^5 are connected by C(=O), $S(=O)_n$ wherein n = 1 or 2, $-CR^{20}R^{17}-$, CR^{20}(-Y- therapeutic agent)-, $-CR^{20}$(-therapeutic agent)-

R^6, R^8 = independently H
(C_1-C_6)alkyl
(C_1-C_6)alkenyl
(C_1-C_6)alkynyl
(C_3-C_{10})cycloalkyl
(C_1-C_9)heterocycloalkyl
(C_6-C_{10})aryl
(C_1-C_9)heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, (C_1-C_4)alkyl, (C_1-C_4)alkenyl, (C_1-C_4)alkynyl, (C_3-C_7)cycloalkyl, (C_1-C_6)heterocycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_4)alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N-$, $R^{20}C(=O)-$, $R^{20}C(=O)O-$, $R^{20}OC(=O)-$, $R^{20}NHC(=O)-$, $R^{20}C(=O)NH-$, $R^{20}R^{21}NC(=O)-$, and $R^{20}OC(=O)O-$, -Y- therapeutic agent or –therapeutic agent,

or R^6, R^8 = independently $-C(=O)R^{17}$, -Y- therapeutic agent, - therapeutic agent, $-S(=O)2R^{17}$ providing R^{17} is not hydrogen, $-C(=O)NR^{17}R^{18}$,

R^7 = H
(C_1-C_6)alkyl
(C_1-C_6)alkenyl
(C_1-C_6)alkynyl
(C_3-C_{10})cycloalkyl
(C_1-C_9)heterocycloalkyl
(C_6-C_{10})aryl
(C_1-C_9)heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, (C_1-C_4)alkyl, (C_1-C_4)alkenyl, (C_1-C_4)alkynyl, (C_3-C_7)cycloalkyl, (C_1-C_6)heterocycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_4)alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N-$, $R^{20}C(=O)-$, $R^{20}C(=O)O-$, $R^{20}OC(=O)-$,

$R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

or two of each R^6, R^7, R^8 are connected by -C(=O), $S(=O)_n$ wherein n = 1 or 2, $-CR^{20}R^{17}$-, CR^{20}(-Y- therapeutic agent)-, -CR^{20}(-therapeutic agent)-,

R^9 = H

CH_3

Y-therapeutic agent

therapeutic agent

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl,

wherein alkyl, alkenyl, alkynyl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-,

-Y- therapeutic agent or –therapeutic agent,

R^{10} = C(=O)-aryl

therapeutic agent,

H

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl,

wherein alkyl, alkenyl, alkynyl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-,

-Y-therapeutic agent or – therapeutic agent

R^{11}= H

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl,

wherein alkyl, alkenyl, alkynyl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

or R^{11} = -Y- therapeutic agent, - therapeutic agent, $-C(=O)R^{17}$

R^{12}, R^{13} = independently H

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl

$(C_3$-$C_{10})$cycloalkyl

$(C_1$-$C_9)$heterocycloalkyl

$(C_6$-$C_{10})$aryl

$(C_1$-$C_9)$heteroaryl,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

or R^{12}, R^{13} = independently $-C(=O)R^{17}$, -Y- therapeutic agent, - therapeutic agent, $-S(=O)_2R^{17}$ providing R^{17} is not hydrogen, $-C(=O)NR^{17}R^{18}$

R^{14} = therapeutic agent

H

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl

$(C_3$-$C_{10})$cycloalkyl

$(C_1$-$C_9)$heterocycloalkyl

$(C_6$-$C_{10})$aryl

$(C_1$-$C_9)$heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

R^{15} = H

$C(=O)R^{17}$

Y- therapeutic agent,

therapeutic agent,

$S(=O)_2R^{17}$ providing R^{17} is not hydrogen

$C(=O)NR^{17}R^{18}$

$(C_1$-$C_6)$alkyl

$(C_1$-$C_6)$alkenyl

$(C_1$-$C_6)$alkynyl

$(C_3$-$C_{10})$cycloalkyl

$(C_1$-$C_9)$heterocycloalkyl

$(C_6$-$C_{10})$aryl

$(C_1$-$C_9)$heteroaryl,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, $(C_1$-$C_4)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_6)$heterocycloalkyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_9)$heteroaryl, $(C_1$-$C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

R^{16} = independently, H

OR^{17}

OR^{22}

R^{17}, R^{18} = independently H

$(C_1\text{-}C_5)$alkyl

$(C_1\text{-}C_6)$alkenyl

$(C_1\text{-}C_6)$alkynyl

$(C_3\text{-}C_{10})$cycloalkyl

$(C_1\text{-}C_9)$heterocycloalkyl

$(C_6\text{-}C_{10})$aryl

$(C_1\text{-}C_9)$heteroaryl

wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by one to five substituents selected independently from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-, -Y- therapeutic agent or –therapeutic agent,

or provided that connected to a nitrogen, R^{17}, R^{18} may form a cyclic structure of 4 to 7 members (including the nitrogen). R^{17} and R^{18} then can represent a fragment from the type of $-[C(AB)]_m\text{-}\Xi_n\text{-}[C(DE)]_o\text{-}\Psi_p\text{-}[C(GJ)]_q$ wherein m, n, o, p and q independently are 0, 1, 2, 3, 4, 5, or 6, Ξ and Ψ independently are -O-, -S-, -NK- and A, B, D, E, G, J, and K independently are hydrogen, $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$alkenyl, $(C_1\text{-}C_4)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_9)$heteroaryl, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, azido, mercapto, $R^{20}R^{21}N$-, $R^{20}C(=O)$-, $R^{20}C(=O)O$-, $R^{20}OC(=O)$-, $R^{20}NHC(=O)$-, $R^{20}C(=O)NH$-, $R^{20}R^{21}NC(=O)$-, and $R^{20}OC(=O)O$-

R^{20}, R^{21} = independently H

$(C_1\text{-}C_6)$alkyl

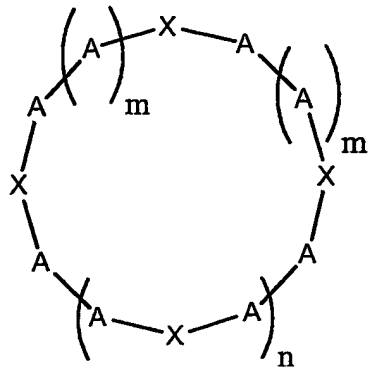
R^{22} = independently, $C(=O)R^{17}$

Y- therapeutic agent

therapeutic agent,

$S(=O)_2R^{17}$ providing R^{17} is not hydrogen, $-C(=O)NR^{17}R^{18}$.

12. The compound of claim 1, wherein the compound is



wherein:

m = independently, 0, 1, 2, 3

n = 0 – 7

X = independently, O

S

Se

NR^1

PR^1

with the proviso, that at least one X = $-NR^1-$

A = independently, CH_2

CHR^2

CR^2R^3

C(=O)

with the proviso, that at least one X = $-NR^1-$ is not an amide

R^1 = independently, H

(C_1-C_{10})alkyl, optionally substituted by fluoro, cyano, R^4, R^4O_2C, $R^4C(=O)NH$ and $R^4S(=O)_k$ wherein k is 0,1 or 2

$R^4C(=O)$, $R^4S(=O)_k$ wherein k is 0, 1 or 2

R^2, R^3 = independently NH_2

NHR^1

NR^1R^5

OH,

OR^4

$R^4C(=O)$ $(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_{12})$alkenyl

$(C_2\text{-}C_{12})$alkynyl

$(C_3\text{-}C_{10})$cycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_9)$heterocycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups are optionally substituted by one to three halo, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, $-C(=O)\text{-}OR^8$, $-C(=O)N(H)R^8$, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $N^*R^5R^6R^7$ wherein * is no or a positive charge, one or two of R^2, R^3 can be a directly coupled therapeutic agent,

R^4 = independently,

NH_2

NHR^9

NR^9R^5

OH

OR^9

$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_{12})$alkenyl

$(C_2\text{-}C_{12})$alkynyl

$(C_3\text{-}C_{10})$cycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_9)$heterocycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups are optionally substituted by one to three halo, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, R^8, $-C(=O)\text{-}OR^8$, $-C(=O)N(H)R^8$, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $N^*R^5R^6R^7$ wherein * is no or a positive charge, or

a therapeutic agent,

R^5, R^6 = independently H

$(C_1\text{-}C_6)$, optionally substituted by hydroxy

$(C_6\text{-}C_{10})$aryl

$(C_2\text{-}C_9)$heteroaryl

R^7 = independently,

lone electron pair

CH_3

C_2H_5

C_3H_7

$CH_2\text{-}C_6H_5$

R^8 = independently, therapeutic agent

R^9 = independently,

$(C_1\text{-}C_6)$ alkyl

$(C_2\text{-}C_{12})$alkenyl

$(C_2\text{-}C_{12})$alkynyl

$(C_3\text{-}C_{10})$cycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_2\text{-}C_9)$heterocycloalkyl$(C_1\text{-}C_6)$alkyl

$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl or

$(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups are optionally substituted by one to three halo, $(C_1\text{-}C_4)$alkoxy, hydroxy, nitro, cyano, R^8, $-C(=O)\text{-}OR^8$, $-C(=O)N(H)R^8$, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $N^*R^5R^6R^7$ wherein * is no or a positive charge, or

a therapeutic agent.

13. The compound of claim 1, wherein the linker is

$(C_1\text{-}C_8)$alkyl,

$(C_1\text{-}C_8)$alkenyl,

$(C_1\text{-}C_8)$alkynyl,

$(C_3\text{-}C_{10})$cycloalkyl,

$(C_6\text{-}C_{10})$aryl,

$(C_2\text{-}C_9)$heteroalkyl, or

$(C_2\text{-}C_9)$heteroaryl,

wherein alkyl-, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl spacing elements are optionally substituted by (C_1-C_6)alkyl, 1-4 halogens, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, hydroxy, amino, (C_1-C_4)alkylamino, (C_1-C_4)dialkylamino, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamido, (C_1-C_4)alkylamidocarbonyl, (C_1-C_4)dialkylamidocarbonyl, nitro, cyano, (C_1-C_4)alkylimino, mercapto or (C_1-C_4)alkylmercapto.

14. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-inflammatory agent.

15. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-infectious agent.

16. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-cancer agent.

17. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an allergy-suppressive agent.

18. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an immune-suppressant agent.

19. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an agent for treating a hematopoietic disorder.

20. The compound of claim 1, wherein the non-antibiotic therapeutic agent is an agent for treating a metabolic disease.

21. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

22. A method of treating an inflammatory disorder, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-inflammatory agent.

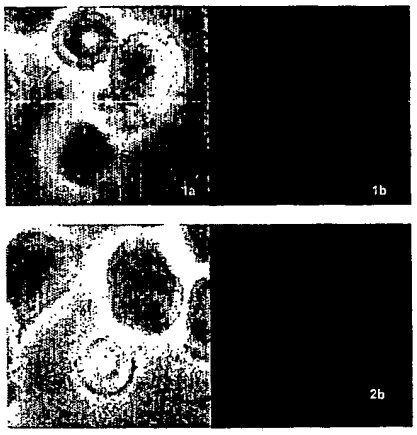
23. A method of treating an infectious disease, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-infectious agent.

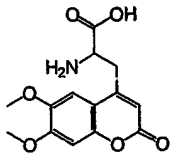
24. A method of treating cancer, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the non-antibiotic therapeutic agent is an anti-cancer agent.

25. A method of treating allergy, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the non-antibiotic therapeutic agent is an allergy-suppressive agent.

26. A method of treating an immune disorder, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the non-antibiotic therapeutic agent is an immune-suppressant agent.

FIG. 1





4

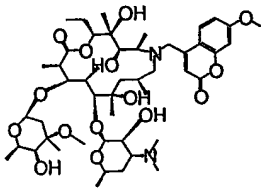


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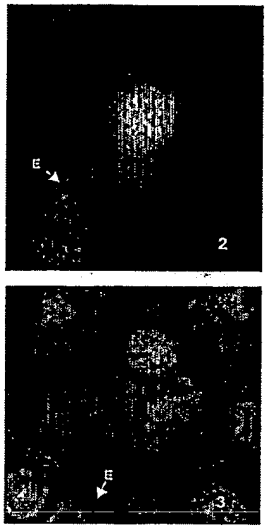
FIG. 2



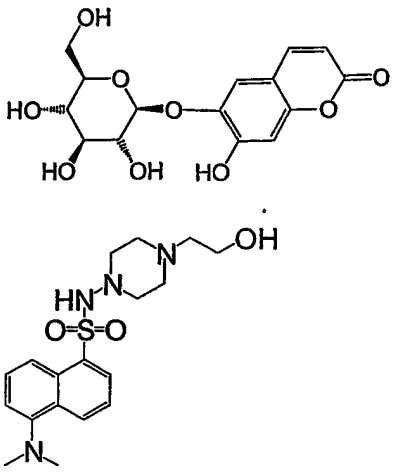


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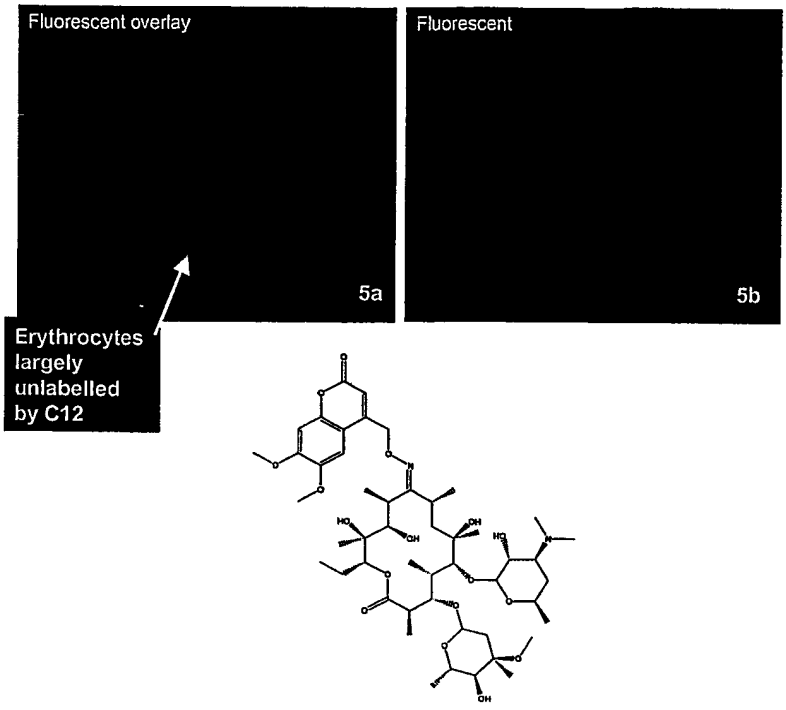
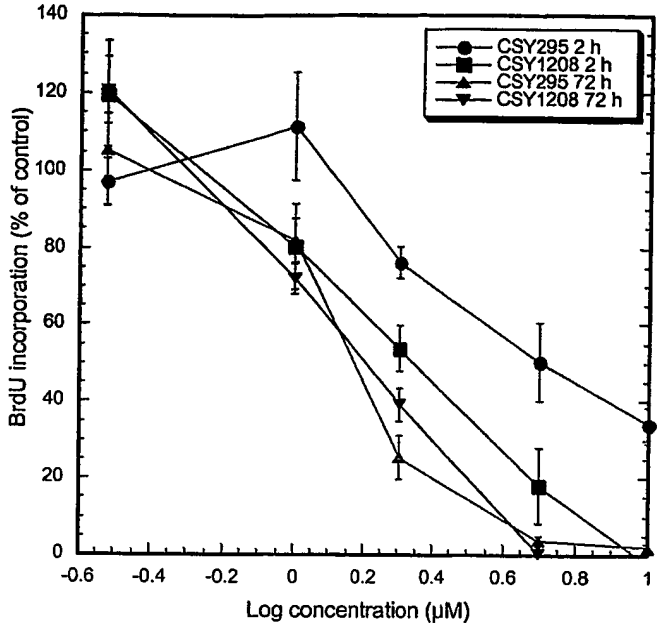
FIG. 3


Fluorescent overlay
5a
Fluorescent
5b
Erythrocytes largely unlabelled by C12

3

FIG. 4


CSY295 2 h
CSY1208 2 h
CSY295 72 h
CSY1208 72 h
BrdU incorporation (% of control)
Log concentration (µM)
140
120
100
80
60
40
20
0
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

5

FIG. 5

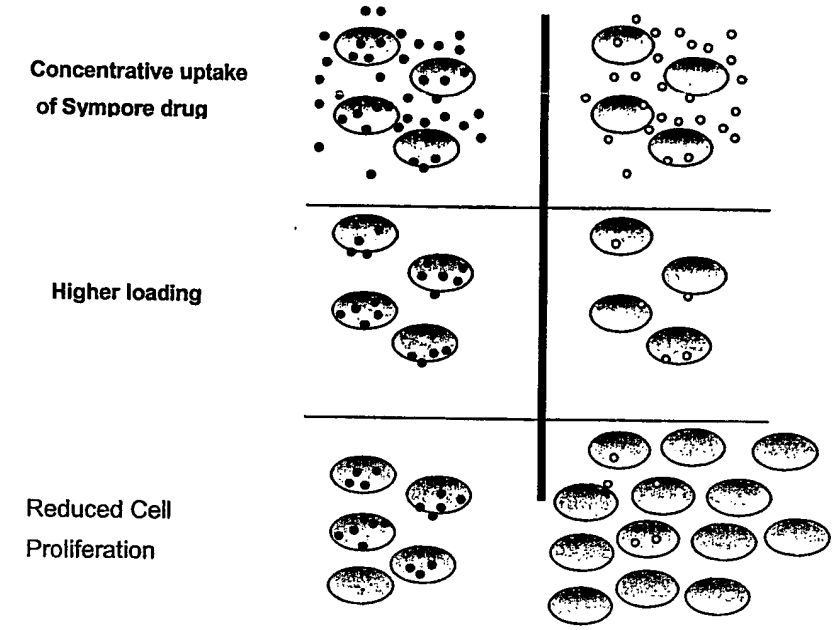
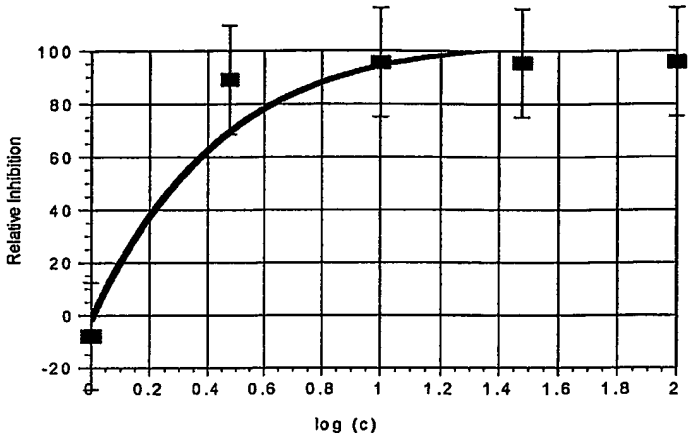

Concentrative uptake
of Sympore drug
Higher loading
Reduced Cell
Proliferation

FIG. 6


Relative Inhibition
100
80
60
40
20
0
-20
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
log (c)

5

FIG. 7

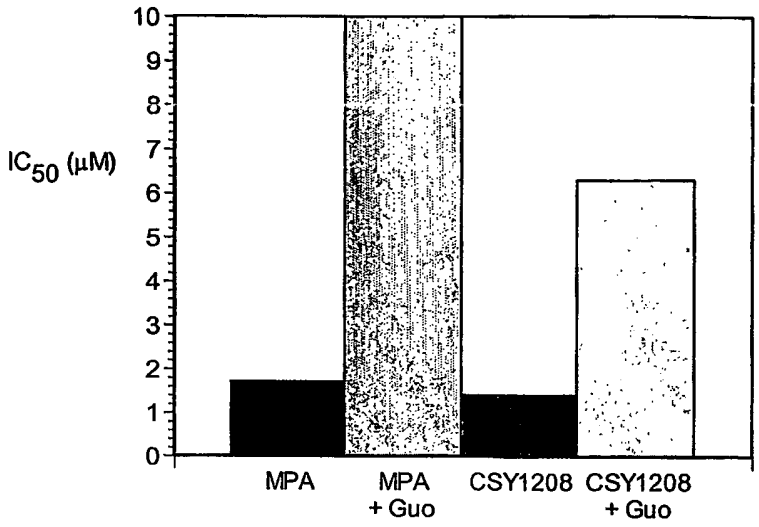


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FIG. 8

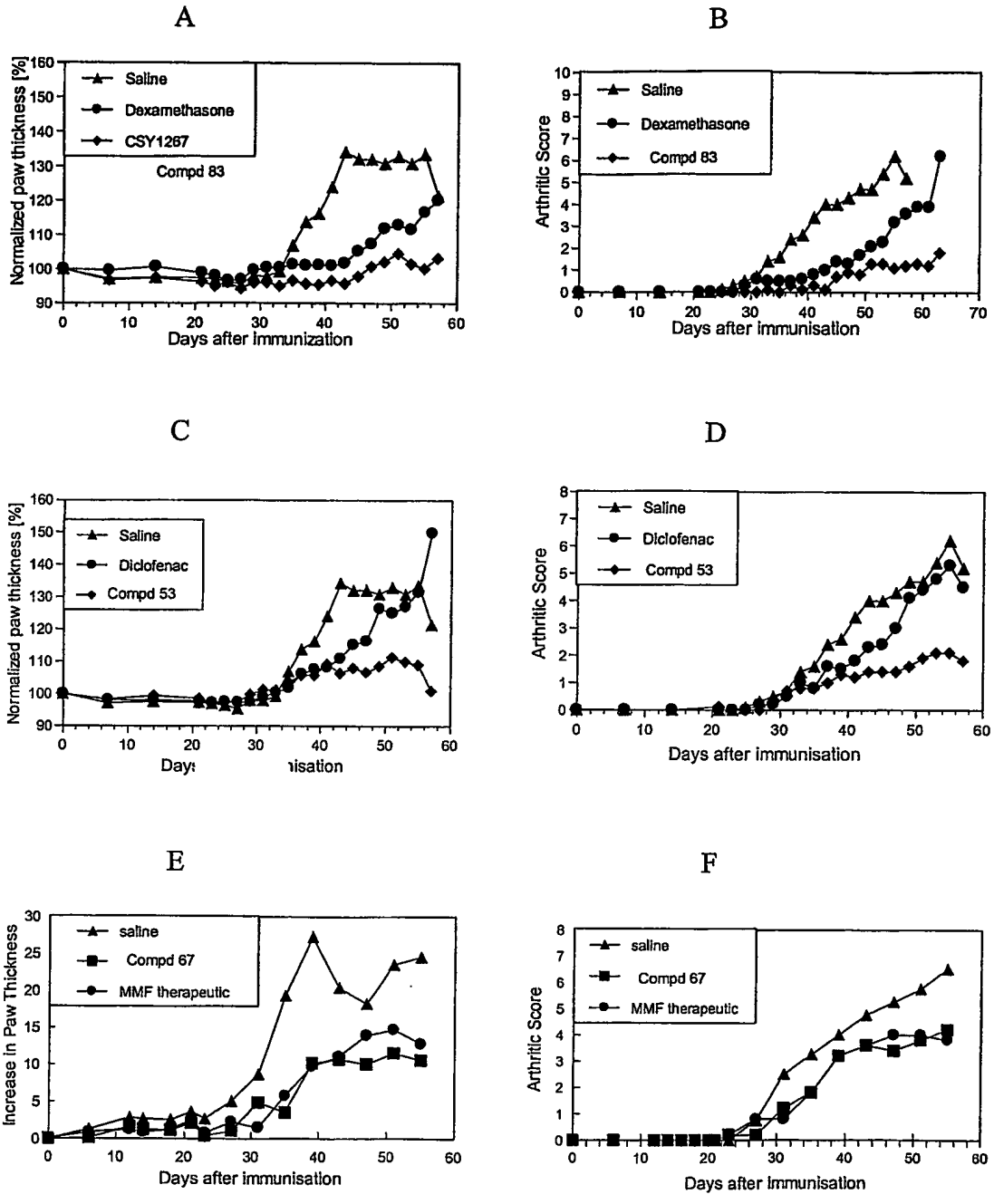

A
Normalized paw thickness [%]
Saline
Dexamethasone
CSY1267
Compd 83
Days after immunization
B
Arthritic Score
Saline
Dexamethasone
Compd 83
Days after immunisation
C
Normalized paw thickness [%]
Saline
Diclofenac
Compd 53
D
Arthritic Score
Saline
Diclofenac
Compd 53
Days after immunisation
E
Increase in Paw Thickness
saline
Compd 67
MMF therapeutic
Days after immunisation
F
Arthritic Score
saline
Compd 67
MMF therapeutic
Days after Immunisation

FIG. 9

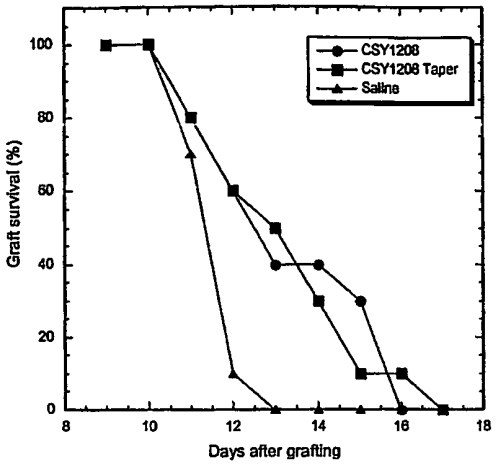
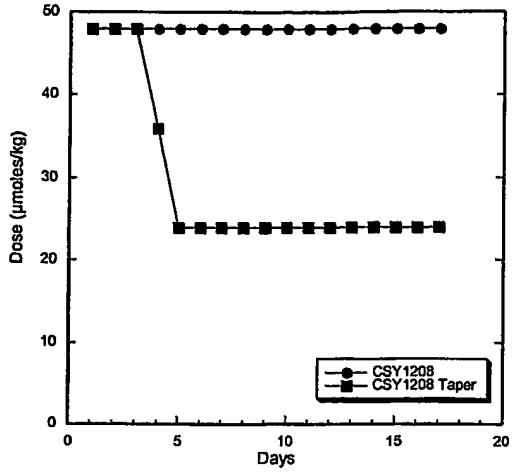

CSY1208
CSY1208 Taper
Saline
Graft survival (%)
Days after grafting
0
20
40
60
80
100
8
10
12
14
16
18

FIG. 10


50
40
30
20
10
0
Dose (µmoles/kg)
0
5
10
15
20
Days
CSY1208
CSY1208 Taper